Reference Example 21

tert-Butyl 2-hydroxyethyl(isopropyl)carbamate

[0371] To a solution (30 mL) of 2-(isopropylamino)ethanol (10.0 g) in tetrahydrofuran was added di-tert-butyl dicarbonate (22.2 g), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure and water (100'mL) was added to the residue. The mixture was extracted with ethyl acetate (200 mL). The ethyl acetate layer was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound (21.21 g) as a colorless oil.
^{1}H-NMR($CDCl_3$): 1.12 (6H,d,J=6. 6Hz), 3.30 (2H,t,J=5.0Hz), 3.71(2H,t,J=5.0Hz), 3.80-4.30(1H,m).

Reference Example 22

2-(Isopropylamino)ethyl acetate hydrochloride

[0372] To a solution (15 mL) of tert-butyl 2-hydroxyethyl(isopropyl)carbamate (5.0 g) obtained in Reference Example 21 in tetrahydrofuran were added pyridine (6.0 mL) and acetic anhydride (2.79 mL) and the mixture was stirred at room temperature for 18 hrs. The reaction mixture was concentrated under reduced pressure, water (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained colorless oil was dissolved in a 4N hydrogen chloride - ethyl acetate solution (10 mL), and the mixture was stirred at room temperature for 1 hr. The precipitated solid was collected by filtration, and dried under reduced pressure to give the title compound (3.14 g) as a colorless solid.
^{1}H-NMR(DMSO-d_6) : 1.25 (6H,d,J=6.6Hz), 2.08 (3H,s), 3.10-3.40(3H,m), 4.29 (2H,t,J=6.0Hz), 9.11(2H,br).

Reference Example 23

Ethyl 2-(isopropylamino)ethyl carbonate hydrochloride

[0373] To a solution (15 mL) of tert-butyl 2-hydroxyethyl(isopropyl)carbamate (5.0 g) obtained in Reference Example 21 in tetrahydrofuran were added pyridine (6.0 mL) and ethyl chlorocarbonate (2.81 mL) and the mixture was stirred at room temperature for 18 hrs. The reaction mixture was concentrated under reduced pressure, and water (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), dried over anhydrous sodium sulfate and the mixture was concentrated under reduced pressure. The obtained colorless oil was dissolved in a 4N hydrogen chloride - ethyl acetate solution (10 mL), and the mixture was stirred at room temperature for 1 hr. The precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (3.34 g) as a colorless solid.
^{1}H-NMR(DMSO-d_6) : 1.20-1.30(9H,m), 3.10-3.40(3H,m), 4.17(2H,q,J=7.4Hz), 4.37(2H,t,J=5.6Hz), 9.13(2H,br).

Reference Example 24

tert-Butyl cyclohexyl(2-hydroxyethyl)carbamate

[0374] To a solution (200 mL) of 2-(cyclohexylamino)ethanol (14.3 g) in ethanol was dropwise added di-tert-butyl dicarbonate (21.8 g). After stirring at room temperature for 2 days, the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL). The mixture was washed with water (100 mL) and saturated brine (100 mL), and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave the title compound (24.2 g) as a colorless oil.
^{1}H-NMR($CDCl_3$) : 1.26-1.39(4H,m), 1.47(9H,s), 1.61-1.81 (6H,m), 3.30-3.40(2H,m), 3.69(2H,t,J=5.4Hz), 3.66-3.90 (2H,br).

Reference Example 25

2-(Cyclohexylamino)ethyl acetate hydrochloride

[0375] To a solution (50 mL) of tert-butyl cyclohexyl(2-hydroxyethyl)carbamate (2.43 g) obtained in Reference Example 24 in tetrahydrofuran were added pyridine (1.05 mL), acetic anhydride (1.23 mL) and 4-dimethylaminopyridine

(0.122 g) under ice-cooling, and the mixture was stirred at room temperature for 12 hrs. Ethyl acetate (100 mL) was added to the reaction mixture and the mixture was washed successively with a saturated aqueous sodium hydrogen carbonate solution (100 mL), a 5% aqueous copper (II) sulfate solution (100 mL) and saturated brine (100 mL), and dried over anhydrous sodium sulfate. The mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (15 mL), and a 4N hydrogen chloride - ethyl acetate solution (15 mL) was added. After stirring at room temperature for 3 hrs., diisopropyl ether (20 mL) was added, and the precipitated solid was collected by filtration to give the title compound (1.78 g) as a white solid.
^{1}H-NMR(DMSO-d_6) : 1.05-2.03 (10H,m), 2.07 (3H,s), 2.90-3.10(1H,m), 3.17(2H,t,J=5.2Hz), 4.29(2H,t,J=5.2Hz), 9.19 (2H,br).

Reference Example 26

2-(Cyclohexylamino)ethyl ethyl carbonate hydrochloride

[0376] To a solution (50 mL) of tert-butyl cyclohexyl(2-hydroxyethyl)carbamate (2.43 g) obtained in Reference Example 24 in tetrahydrofuran were added pyridine (1.45 mL), ethyl chlorocarbonate (1.71 mL) and 4-dimethylaminopyridine (0.122 g) under ice-cooling, and the mixture was stirred at room temperature for 15 hrs. Ethyl acetate (100 mL) was added to the reaction mixture, and the mixture was washed successively with a saturated aqueous sodium hydrogen carbonate solution (100 mL), a 5% aqueous copper (II) sulfate solution (100 mL), water (100 mL) and saturated brine (100 mL), and dried over anhydrous sodium sulfate. The mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (15 mL). A 4N hydrogen chloride - ethyl acetate solution (15 mL) was added. After stirring at room temperature for 3 hrs., diisopropyl ether (20 mL) was added, and the precipitated solid was collected by filtration to give the title compound (2.12 g) as a white solid.
^{1}H-NMR(DMSO-d_6) : 1.01-2.08(10H,m), 1.23 (3H,t,J=7.0Hz), 2.90-3.10 (1H,m), 3.21 (2H,t,J=5.2Hz), 4.16 (2H,q, J=7.0Hz), 4.39 (2H,t,J=5.2Hz), 9.27(2H,br).

Reference Example 27

2-Anilinoethyl acetate hydrochloride

[0377] To a solution (700 mL) of 2-anilinoethanol (137 g) in tetrahydrofuran were added pyridine (97.1 mL), acetic anhydride (113.2 mL) and 4-dimethylaminopyridine (12.22 g) under ice-cooling, and the mixture was stirred at room temperature for 20 hrs. Ethyl acetate (1 L) was added to the reaction mixture and the mixture was washed successively with water (1 L), a saturated aqueous sodium hydrogen carbonate solution (1 L), a 5% aqueous copper (II) sulfate solution (1 L) and saturated brine (1 L), dried over anhydrous sodium sulfate, and evaporated under reduced pressure. To a solution of the obtained residue in ethyl acetate (700 mL) was added a 4N hydrogen chloride - ethyl acetate solution (250 mL) under ice-cooling, and the precipitated solid was collected by filtration to give the title compound (156 g) as a white solid.
^{1}H-MMR(CD_3OD): 2.11 (3H,s), 3.71-3.76 (2H,m), 4.32-4.37 (2H,m), 7.49-7.64(5H,m).

Reference Example 28

tert-Butyl [2-(methylamino)-3-pyridyl]methyl carbonate

[0378] To a solution (50 mL) of [2-(methylamino)-3-pyridyl]methanol (2 g: synthesized according to the method described in WO 01/32652) in tetrahydrofuran were added di-tert-butyl dicarbonate (3.48 g) and 4-dimethylaminopyridine (0.18 g) and the mixture was refluxed for 1 hr. Water (30 mL) was added to the reaction mixture and the mixture was extracted with ethyl acetate (50 mL). The obtained organic layer was washed with saturated brine (50 mL), and dried over anhydrous sodium sulfate. The residue obtained by concentration under reduced pressure was purified by flash silica gel column chromatography (eluted with ethyl acetate:hexane=1:5) to give the title compound (1.51 g) as a white solid.
^{1}H-NMR($CDCl_3$) : 1.49 (9H,s), 3.02 (3H,d,J=4.8Hz), 4.99 (2H,s), 5.00 (1H,bs), 6.55 (1H,dd,J=7.0,5.0Hz), 7.37 (1H,dd, J=7.0,1.8Hz), 8.16 (1H,dd,J=5.0,1.8Hz).

Reference Example 29

2-(Methylamino)benzyl acetate

[0379] To a solution (50 mL) of [2-(methylamino)phenyl]methanol (1.37 g: synthesized according to the method described in WO 01/32652) in tetrahydrofuran were added pyridine (1.05 mL), acetic anhydride (1.23 mL) and 4-dimethylaminopyridine (0.18 g), and the mixture was stirred at room temperature for 8 hrs. Water (100 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (100 mL). The organic layer was washed successively with a 5% aqueous copper (II) sulfate solution (50 mL), a saturated aqueous sodium hydrogen carbonate solution (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by flash silica gel column chromatography (eluted with ethyl acetate: hexane=1:5, then 1:3) to give the title compound (0.38 g) as a white solid.
^{1}H-NMR($CDCl_3$) : 2.08 (3H,s), 2.87 (3H,s), 4.40 (1H,br), 5.08 (2H,s), 6.64-6.74(2H,m), 7.17-7.32(2H,m).

Reference Example 30

2-[(2-Acetyloxyethyl)amino]ethyl acetate hydrochloride

[0380] To a mixture of 2,2'-iminodiethanol (2.10 g) and ethyl acetate (20 mL) was added di-tert-butyl dicarbonate (4.37 g) under ice-cooling. After stirring for 1.5 hrs. under ice-cooling, acetic anhydride (2.08 mL), pyridine (1.78 mL) and 4-dimethylaminopyridine (0.12 g) were added. After stirring at room temperature for 2 hrs., ethyl'acetate (50 mL) was added to the reaction mixture and the mixture was washed with water (50 mL), a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL). After drying over anhydrous magnesium sulfate, the mixture was concentrated under reduced pressure. A 4N hydrogen chloride - ethyl acetate solution (20 mL) was added to the residue, and the mixture was stirred at room temperature for 2 hrs. Diethyl ether (10 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (6.18 g) as a white solid.
^{1}H-NMR(DMSO-d_6) : 2.07 (6H,s), 3.23 (4H,t,J=5.3Hz), 4.27-4.33(4H,m), 9.40 (2H,br).

Reference Example 31

(S)-2-Pyrrolidinylmethyl acetate hydrochloride

[0381] To a mixture of (S)-2-pyrrolidinylmethanol (1.01 g) and ethyl acetate (10 mL) was added di-tert-butyl dicarbonate (2.18 g) under ice-cooling. After stirring for 1 hr. under ice-cooling, acetic anhydride (1.04 mL), pyridine (0.89 mL) and 4-dimethylaminopyridine (0.061 g) were added. After stirring at room temperature for 1 hr., ethyl acetate (50 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL), a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL). After drying over anhydrous magnesium sulfate, the mixture was concentrated under reduced pressure. A 4N hydrogen chloride - ethyl acetate solution (10 mL) was added to the residue, and the mixture was stirred at room temperature for 1 hr. Diethyl ether (10 mL) was added and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (1.68 g) as a pale-brown solid.
^{1}H-NMR (DMSO-d_6) : 1.56-2.10 (4H,m), 2.06 (3H,s), 3.05-3.24 (2H,m), 3.63-3.68 (1H,m), 4.15 (1H,dd,J=11.8,8.1Hz), 4.26 (1H,dd,J=11.8,4.1Hz), 9.21 (1H,br), 9.87 (1H,br).

Reference Example 32

3-(Methylamino)propyl benzoate hydrochloride

[0382] To a mixture of 3-amino-1-propanol (0.75 g) and ethyl acetate (2.25 mL) was added a solution (0.25 mL) of di-tert-butyl dicarbonate (2.18 g) in ethyl acetate under ice-cooling. After stirring at room temperature for 21.5 hrs., benzoyl chloride (1.30 mL), pyridine (0.98 mL) and 4-dimethylaminopyridine (0.012 g) were added. After stirring at room temperature for 5 hrs., ethyl acetate (32.5 mL) was added to the reaction mixture, and the mixture was washed with water (12.5 mL) and saturated brine (12.5 mL). After drying over anhydrous magnesium sulfate, the mixture was concentrated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (20 mL), and methyl iodide (5 mL) was added. 60% Sodium hydride (0.4 g) was added under ice-cooling. After stirring at room temperature for 3 hrs., the reaction mixture was poured into an ice-cooled aqueous ammonium chloride solution (60 mL). The mixture was extracted with diethyl ether (80 mL). The extract was washed with saturated brine (30 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column

chromatography (ethyl acetate:hexane=2:1, then ethyl acetate, then acetone:ethyl acetate=1:9) to give 3-[(tert-butoxycarbonyl)(methyl)amino]propyl benzoate (2.52 g) as a colorless oil. A 4N hydrogen chloride - ethyl acetate solution (10 mL) was added, and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, ethyl acetate (10 mL) was added to the residue and the precipitated solid was collected by filtration. After washing with diethyl ether (10 mL), the solid was dried under reduced pressure to give the title compound (1.73 g) as a colorless solid.

^{1}H-NMR (DMSO-d_6) : 2.02-2.16 (2H,m), 2.56 (3H, s), 3.05(2H,t,J=7.3Hz), 4.35 (2H,t,J=6.1Hz), 7.51(2H,m), 7.65-7.73 (1H,m), 8.01 (2H,d,J=7.2Hz), 8.95(2H,br).

Reference Example 33

2-[(Ethoxycarbonyl)(methyl)amino]ethyl ethyl carbonate

[0383] To a solution (1000 mL) of 2-(methylamino)ethanol (100 g) in ethyl acetate was added pyridine (222 mL), ethyl chlorocarbonate (240 mL) was dropwise added over 2 hr. under ice-cooling. After the completion of the dropwise addition, the reaction mixture was stirred at room temperature for 18 hrs. Water (300 mL) was added, and the ethyl acetate layer was separated and washed with 1N hydrochloric acid (200 mL) and saturated brine (200 mL). After drying over anhydrous sodium sulfate, the layer was concentrated under reduced pressure, and the residue was distilled under reduced pressure to give the title compound (180 g) as a colorless fraction having a boiling point of 95-100°C (pressure: 0.1-0.2 mmHg).

^{1}H-NMR ($CDCl_3$) : 1.20-1.40 (6H,m), 2.97(3H,s), 3.50-3.60 (2H,m), 4.05-4.35 (6H,m).

Reference Example 34

2-[(Chlorocarbonyl)(methyl)amino]ethyl ethyl carbonate

[0384] To a solution (1500 mL) of 2-[(ethoxycarbonyl) (methyl)amino]ethyl ethyl carbonate (150 g) obtained in Reference Example 33 in acetonitrile was added phosphorus oxychloride (200 mL), and the mixture was refluxed for 4 days. The reaction mixture was concentrated under reduced pressure and the residue was added to a mixture of water (500 mL) - ice (700 g) - ethyl acetate (300 mL) by portions with stirring. After stirring for 1 min., saturated brine (500 mL) was added, and the mixture was extracted with ethyl acetate (500 mL). The ethyl acetate layer was washed successively with saturated brine (300 mL), a saturated aqueous sodium hydrogen carbonate solution (300 mL) and saturated brine (300 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was distilled under reduced pressure to give the title compound (77 g) as a colorless fraction having a boiling point of 100-105°C (pressure: 0. 1-0.2 mmHg).

^{1}H-NMR($CDCl_3$) : 1.33 (3H,t,J=7.2Hz), 3.12 (3H×0.4, s), 3.22(3H×0.6,s), 3.68(2H×0.6, t, J=4.8Hz), 3.78(2H×0.4,t, J=4.8Hz), 4.23(2H,q,J=7.2Hz), 4.30-4.40(2H,m).

Reference Example 35

tert-Butyl 4-hydroxybutylcarbamate

[0385] To a mixture of 4-aminobutanol (3.57 g) and ethyl acetate (9 mL) was dropwise added a mixture of di-tert-butyl dicarbonate (8.73 g) and ethyl acetate (1 mL) under ice-cooling. After stirring at room temperature for 24 hrs., the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL), and the mixture was washed with water (50 mL), 1N hydrochloric acid (40 mL), water (30 mL) and saturated brine (30 mL) and dried over anhydrous magnesium sulfate. Concentration under reduced pressure gave the title compound (7.54 g) as a colorless oil.

^{1}H-NMR($CDCl_3$) : 1.44 (9H,s), 1.47-1.61 (4H,m), 3.07-3.22 (2H,m), 3.61-3.76(2H,m), 4.62 (1H,bs).

Reference Example 36

4-[(tert-Butoxycarbonyl)amino]butyl acetate

[0386] To a mixture of tert-butyl 4-hydroxybutylcarbamate (3.83 g) obtained in Reference Example 35 and ethyl acetate (20 mL) were added pyridine (1.80 mL) and acetic anhydride (2.27 g), and the mixture was stirred at room temperature for 19 hrs. Ethyl acetate (100 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL), an aqueous copper sulfate solution (30 mL), water (30 mL) and saturated brine (30 mL) and dried over

anhydrous magnesium sulfate. Concentration under reduced pressure gave the title compound (4.55 g) as a colorless oil.
^{1}H-NMR($CDCl_3$): 1.44 (9H,s), 1.51-1.69 (4H,m), 2.05 (3H,s), 3.15(2H,m), 4.07 (2H,t,J=6.5Hz), 4.55 (1H,bs).

Reference Example 37

4-(Methylamino)butyl acetate hydrochloride

[0387] To a solution (20 mL) of 4-[(tert-butoxycarbonyl)amino]butyl acetate (4.50 g) obtained in Reference Example 36 and methyl iodide (4.85 mL) in N,N-dimethylformamide was added sodium hydride (60% in oil, 0.94 g) under ice-cooling. After stirring at room temperature for 4 hrs., the reaction mixture was poured into an ice - aqueous ammonium chloride solution. The mixture was extracted with diethyl ether (120 mL), and the diethyl ether layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:9). To the purified product was added a 4N hydrogen chloride - ethyl acetate solution (20 mL), and the mixture was stirred at room temperature for 2 hrs. Diethyl ether (40 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (2.28 g) as a white solid.
^{1}H-NMR(DMSO-d_6) : 1.58-1.70 (4H,m), 2.01(3H,s), 2.50(3H,s), 2.82-2.90(2H,m), 4.00(2H,t,J=6.0Hz), 8.90(2H,br).

Reference Example 38

4-[(tert-Butoxycarbonyl)amino]butyl ethyl carbonate

[0388] To a mixture of tert-butyl 4-hydroxybutylcarbamate (3.71 g) obtained in Reference Example 35 and ethyl acetate (20 mL) were added pyridine (1.71 mL) and ethyl chlorocarbonate (2.55 g) under ice-cooling, and the mixture was stirred at room temperature for 24 hrs. Ethyl acetate (100 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL), an aqueous copper sulfate solution (30 mL), water (30 mL) and saturated brine (30 mL) and dried over anhydrous magnesium sulfate. Concentration under reduced pressure gave the title'compound (4.92 g) as a colorless oil.
^{1}H-NMR ($CDCl_3$) : 1.31 (3H,t,J=7.1Hz), 1.44 (9H,s), 1.46-1.80(4H,m), 3.15 (2H,m), 4.11-4.25 (4H,m), 4.54 (1H,bs).

Reference Example 39

Ethyl 4-(methylamino)butyl carbonate hydrochloride

[0389] To a solution (20 mL) of 4-[(tert-butoxycarbonyl)amino]butyl ethyl carbonate (4.90 g) obtained in Reference Example 38 and methyl iodide (4.67 mL) in N,N-dimethylformamide was added sodium hydride (60% in oil, 0.90 g) under ice-cooling. After stirring at room temperature for 6 hrs., the reaction mixture was poured into an ice - aqueous ammonium chloride solution, and extracted with diethyl ether (120 mL). The diethyl ether layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:9). To the purified product was added a 4N hydrogen chloride - ethyl acetate solution (20 mL), and the mixture was stirred at room temperature for 2 hrs. Diethyl ether (40 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (2.86 g) as a white solid.
^{1}H-NMR(DMSO-d_6) : 1.21 (3H,t,J=7.1Hz), 1.51-1.73 (4H,m), 2. 50 (3H, s), 2. 82-2. 94 (2H,m), 4. 05-4. 15 (4H,m), 8. 88 (2H,br).

Reference Example 40

tert-Butyl 3-hydroxypropylcarbamate

[0390] To a mixture of 3-aminopropanol (7.51 g) and ethyl acetate (30 mL) was dropwise added a mixture of di-tert-butyl dicarbonate (21.8 g) and ethyl acetate (3 mL) under ice-cooling. After stirring at room temperature for 22 hrs., the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL), washed with water (80 mL), 1N hydrochloric acid (60 mL), water (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave the title compound (16.01 g) as a colorless oil.
^{1}H-NMR($CDCl_3$): 1.45(9H,s), 1.62-1.70 (2H,m), 3.24(2H,q,J=6.6Hz), 3.66(2H,q,J=5.1Hz), 4.73(1H,bs).

Reference Example 41

3-[(tert-Butoxycarbonyl)amino]propyl acetate

[0391] To a mixture of tert-butyl 3-hydroxypropylcarbamate (8.00 g) obtained in Reference Example 40 and ethyl acetate (50 mL) were added pyridine (4.06 mL) and acetic anhydride (5.13 g), and the mixture was stirred at room temperature for 21 hrs. Ethyl acetate (200 mL) was added to the reaction mixture, and the mixture was washed with water (100 mL), an aqueous copper sulfate solution (40 mL), water (60 mL) and saturated brine (60 mL), and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave the title compound (8.34 g) as a colorless oil.
^{1}H-NMR ($CDCl_3$) : 1.44 (9H,s), 1.77-1.86 (2H,m), 2.06 (3H,s), 3.20(2H,q,J=6.3Hz), 4.12(2H,t,J=6.3Hz), 4.67 (1H,bs).

Reference Example 42

3-(Methylamino)propyl acetate hydrochloride

[0392] To a solution (80 mL) of 3-[(tert-butoxycarbonyl)amino]propyl acetate (17.28 g) obtained in Reference Example 41 and methyl iodide (19.8 mL) in N,N-dimethylformamide was added sodium hydride (60% in oil, 3.82 g) under ice-cooling. After stirring at room temperature for 15 hrs., the reaction mixture was poured into an ice - aqueous ammonium chloride solution and extracted with diethyl ether (300 mL). The diethyl ether layer was washed with saturated brine (100 mL), and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:8). To the purified product was added a 4N hydrogen chloride - ethyl acetate solution (40 mL), and the mixture was stirred at room temperature for 2 hrs. Diethyl ether (100 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (2.93 g) as a white solid.
^{1}H-NMR(DMSO-d_6) : 1.85-1.97 (2H,m), 2.02 (3H,s), 2.50 (3H,s), 2.87-2.96(2H,m), 4.06 (2H,t,J=6.3Hz), 8. 87 (2H,br).

Reference Example 43

3-[(tert-Butoxycarbonyl)amino]propyl ethyl carbonate

[0393] To a mixture of tert-butyl 3-hydroxypropylcarbamate (8.00 g) obtained in Reference Example 40 and ethyl acetate (50 mL) were added pyridine (4.06 mL) and ethyl chlorocarbonate (5.95 g) under ice-cooling, and the mixture was stirred at room temperature for 24 hrs. Ethyl acetate (100 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL), an aqueous copper sulfate solution (30 mL), water (30 mL) and saturated brine (30 mL), and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave the title compound (9.31 g) as a colorless oil.
^{1}H-NMR($CDCl_3$) : 1.31(3H,t,J=7.1Hz), 1.44(9H,s), 1.82-1.90(2H,m), 3.22(2H,t,J=6.3Hz), 4.15-4.23(4H,m), 4.68(1H, bs).

Reference Example 44

Ethyl 3-(methylamino)propyl carbonate hydrochloride

[0394] To a solution (40 mL) of 3-[(tert-butoxycarbonyl)amino]propyl ethyl carbonate (9.31 g) obtained in Reference Example 43 and methyl iodide (9.00 mL) in N,N-dimethylformamide was added sodium hydride (60% in oil, 1.82 g) under ice-cooling. After stirring at room temperature for 12 hrs., the reaction mixture was poured into an ice - aqueous ammonium chloride solution and the mixture was extracted with diethyl ether (200 mL). The diethyl ether layer was washed with saturated brine (100 mL), and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:8). To the purified product was added a 4N hydrogen chloride - ethyl acetate solution (40 mL), and the mixture was stirred at room temperature for 2 hrs. Diethyl ether (200 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (4.98 g) as a white solid.
^{1}H-NMR(DMSO-d_6) : 1.21 (3H, t, J=7. 1Hz), 1.91-2.00 (2H, m), 2.50(3H,s), 2.88-2.98(2H,m), 4.08-4.16 (4H,m), 8.90 (2H,br).

Reference Example 45

tert-Butyl (2,3-dihydroxypropyl)methylcarbamate

[0395] To a mixture of 3-(methylamino)-1,2-propanediol (24.5 g) and ethyl acetate (50 mL) was dropwise added a mixture of di-tert-butyl dicarbonate (51.4 g) and ethyl acetate (10 mL) under ice-cooling. After stirring at room temperature for 15 hrs., the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (150 mL), and the solution was washed with water (80 mL), 1N hydrochloric acid (60 mL), water (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave the title compound (26.9 g) as a colorless oil.
^{1}H-NMR ($CDCl_3$) : 1.47(9H,s), 2.92(3H,s), 3.20-3.36(2H,m), 3.41(2H,bs), 3.50-3.62(2H,m), 3.73-3.88(1H,m).

Reference Example 46

3-(Methylamino)propane-1,2-diyl diacetate hydrochloride

[0396] To a mixture of tert-butyl (2,3-dihydroxypropyl)methylcarbamate (10.26 g) obtained in Reference Example 45 and ethyl acetate (50 mL) were added pyridine (10.11 mL) and acetic anhydride (12.76 g), and the mixture was stirred at room temperature for 24 hrs. Ethyl acetate (300 mL) was added to the reaction mixture, and the mixture was washed with water (150 mL), an aqueous copper sulfate solution (100 mL), water (100 mL) and saturated brine (100 mL), and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:8). To the purified product was added a 4N hydrogen chloride - ethyl acetate solution (40 mL), and the mixture was stirred at room temperature for 3 hrs. Diethyl ether (100 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (2.76 g) as a white solid.
^{1}H-NMR (DMSO-d_6) : 2.03 (3H, s), 2.07 (3H, s), 2.55 (3H, s), 3.18-3.22(2H,m), 4.09-4.28 (2H,m), 5.20-5.27 (1H,m), 9.01 (2H,br).

Reference Example 47

Diethyl 3-(methylamino)propane-1,2-diyl biscarbonate hydrochloride

[0397] To a mixture of tert-butyl (2,3-dihydroxypropyl)methylcarbamate (15.53 g) obtained in Reference Example 45 and ethyl acetate (100 mL) were added pyridine (18.35 mL) and ethyl chlorocarbonate (24.62 g) under ice-cooling, and the mixture was stirred at room temperature for 96 hrs. Ethyl acetate (300 mL) was added to the reaction mixture, and the mixture was washed with water (150 mL), an aqueous copper sulfate solution (100 mL), water (100 mL) and saturated brine (100 mL), and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:6). To the purified product was added a 4N hydrogen chloride - ethyl acetate solution (80 mL), and the mixture was stirred at room temperature for 3 hrs. Diethyl ether (200 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (5.93 g) as a white solid. ^{1}H-NMR(DMSO-d_6) : 1.20-1.28 (6H,m), 2.57 (3H,s), 3.12-3.28(2H,m), 4.10-4.43 (6H,m), 5.13-5.22 (1H,m), 9.14 (2H,br).

Reference Example 48

2-Ethoxyethyl 2-(methylamino)ethyl carbonate hydrochloride

[0398] To a solution (20 mL) of bis(trichloromethyl)carbonate (2.97 g) in tetrahydrofuran was dropwise added a solution (10 mL) of 2-ethoxyethanol (1.80 g) in tetrahydrofuran under ice-cooling. Then a solution (10 mL) of pyridine (2.43 mL) in tetrahydrofuran was added dropwise, and the mixture was stirred at room temperature for 2 hrs. The reaction mixture was concentrated under reduced pressure and water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 2-ethoxyethyl chlorocarbonate (1.29 g). A solution (15 mL) of tert-butyl 2-hydroxyethyl(methyl)carbamate (1.23 g) obtained in Reference Example 1 in tetrahydrofuran was added pyridine (0.68 mL), and a solution (5 mL) of 2-ethoxyethyl chlorocarbonate obtained above in tetrahydrofuran was dropwise added to the mixture, and the mixture was stirred at room temperature for 3 days. After concentration of the reaction mixture under reduced pressure, water (50 mL) was added thereto and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with a

5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), dried over anhydrous magnesium sulfate. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:5, then 2:3). The purified product (1.60 g) was dissolved in diethyl ether (3 mL) and a 4N hydrogen chloride - ethyl acetate solution (3 mL) was added. The mixture was stirred overnight at room temperature, and the precipitated solid was collected by filtration and dried under reduced pressure to give the title compound (0.94 g) as a while solid.

^{1}H-NMR(DMSO-d_6) : 1.10 (3H,t,J=7.0Hz), 2.57 (3H,s), 3.18-3.25(2H,m), 3.44(2H,q,J=7.0Hz), 3.56-3.60(2H,m), 4.19-4. 24 (2H,m), 4.30-4.37 (2H,m), 8.79 (2H,br).

Reference Example 49

3-Methoxypropyl 2-(methylamino)ethyl carbonate hydrochloride

[0399] To a mixture of lithium aluminum hydride (2.85 g) and diethyl ether (100 mL) was dropwise added slowly a solution (50 mL) of methyl 3-methoxypropanoate (11.8 g) in tetrahydrofuran under ice-cooling. After stirring at room temperature for 1 hr., the mixture was again ice-cooled and water (3 mL) and a 10% aqueous sodium hydroxide solution (3 mL) were dropwise added. The mixture was allowed to reach room temperature, and water (9 mL) was dropwise added. The mixture was stirred for a while. The precipitate was filtered off and the filtrate was concentrated under reduced pressure to give 3-methoxypropanol (7.64 g) as a colorless oil.

^{1}H-NMR($CDCl_3$) : 1. 83 (2H,quintet,J=5.8Hz), 2.43 (1H,t,J=5.3Hz), 3.36(3H,s), 3.57(2H,t,J=6.0Hz), 3.77(2H,q, J=5.5Hz).

[0400] To a solution (50 mL) of bis(trichloromethyl)carbonate (4.45 g) in tetrahydrofuran was dropwise added N-ethyldiisopropylamine (5.75 mL) under ice-cooling. After stirring for a while, a solution (15 mL) of 3-methoxypropanol (2.70 g) obtained above in tetrahydrofuran was dropwise added. The mixture was stirred for 30 min. under ice-cooling and at room temperature for 1 day. After concentration of the reaction mixture under reduced pressure, diluted hydrochloric acid (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (30 mL) and saturated brine (30 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 3-methoxypropyl chlorocarbonate (4.39 g). To a solution (20 mL) of tert-butyl 2-hydroxyethyl(methyl)carbamate (1.75 g) obtained in Reference Example 1 in tetrahydrofuran was added pyridine (0.97 mL) and a solution (5 mL) of a 3-methoxypropyl chlorocarbonate (1.83 g) obtained above in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. A solution (5 mL) of pyridine (0.65 mL) and 3-methoxypropyl chlorocarbonate (1.22 g) in tetrahydrofuran was added and the mixture was further stirred for 1 hr. The reaction mixture was concentrated under reduced pressure and water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (80 mL), and the ethyl acetate layer was washed with a 5% aqueous citric acid solution (50 mL) and saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:9, then 3:7). The purified product (3.40 g) was dissolved in diethyl ether (5 mL) and a 4N hydrogen chloride - ethyl acetate solution (5 mL) was added. The mixture was stirred overnight at room temperature and the reaction mixture was concentrated under reduced pressure. Diethyl ether was added for crystallization to give the title compound (2.06 g) as a colorless solid.

^{1}H-NMR (DMSO-d_6) : 1.78-1.90 (2H,m), 2.54 (3H, s), 3.15-3.25 (2H,m), 3.23(3H,s), 3.33-3.42(2H,m), 4.16(2H,t, J=6.0Hz), 4.36(2H,t,J=6.0Hz), 9.27 (2H,br).

Reference Example 50

2-(Methylamino)ethyl N,N-dimethylglycinate dihydrochloride

[0401] A mixture of tert-butyl 2-hydroxyethyl(methyl)carbamate (3.50 g) obtained in Reference Example 1, N,N-dimethylglycine hydrochloride (5.29 g), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (7.67 g), triethylamine (5.58 mL), 4-dimethylaminopyridine (1.22 g) and N,N-dimethylformamide (50 mL) was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and a saturated aqueous sodium hydrogen carbonate solution (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with methanol:ethyl acetate=5:95, then 20:80). 1N Hydrochloric acid (24 mL) was added to the purified product (2.46 g), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to give the title compound (2.14 g) as a colorless solid.

^{1}H-NMR(DMSO-d_6) : 2.52 (3H,s), 2.85 (6H,s), 3.20 (2H,m), 4.30(2H,s), 4.43-4.49(2H,m), 9.60(2H,br), 10. 81 (1H,br).

Reference Example 51

S-[2-(Methylamino)ethyl] thioacetate hydrochloride

[0402] To a solution (50 mL) of tert-butyl 2-hydroxyethyl(methyl)carbamate (3.50 g) obtained in Reference Example 1, thioacetic acid (1.72 mL) and triphenylphosphine (7.87 g) in tetrahydrofuran was dropwise added slowly a solution (10 mL) of diisopropyl azodicarboxylate (5.91 mL) in tetrahydrofuran under ice-cooling. The mixture was stirred under ice-cooling for 1 hr. and at room temperature for 2 hrs. The reaction mixture was again ice-cooled and a solution (10 mL) of triphenylphosphine (7.87 g) and diisopropyl azodicarboxylate (5.91 mL) in tetrahydrofuran was added. The mixture was stirred under ice-cooling for 30 min. Thioacetic acid (1.14 mL) was added and the mixture was stirred under ice-cooling for 30 min. and at room temperature overnight. The reaction mixture was concentrated under reduced pressure and hexane and diisopropyl ether were added to the residue. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. This step was repeated and a saturated aqueous sodium hydrogen carbonate solution (50 mL) was added. The mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=5:95, and then 15:85). A 4N hydrogen chloride - ethyl acetate solution (10 mL) was added to the purified product (4.47 g) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and ethyl acetate and diethyl ether were added to the residue for crystallization to give the title compound (1.79 g) as a pale-yellow solid.
^{1}H-NMR (DMSO-d_6) : 2.38(3H,s), 2.52 (3H, s), 2.96-3.08(2H,m), 3.12-3.20(2H,m), 9.35(2H,br).

Reference Example 52

Ethyl 2-[2-(methylamino)ethoxy]ethyl carbonate hydrochloride

[0403] To a mixture of 2-(2-aminoethoxy)ethanol (99.52 g) and ethyl acetate (200 mL) was dropwise added a mixture of di-tert-butyl dicarbonate (208.57 g) and ethyl acetate (50 mL) under ice-cooling. After stirring at room temperature for 60 hrs., the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (500 mL), washed with water (200 mL), 1N hydrochloric acid (200 mL), water (300 mL) and saturated brine (300 mL), and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave tert-butyl [2-(2-hydroxyethoxy)ethyl] carbamate (169.2 g) as a colorless oil.
^{1}H-NMR ($CDCl_3$) : 1.45 (9H,s), 3.33 (2H,q,J=5.1Hz), 3.54-3.59(4H,m), 3.74 (2H,q,J=5.1Hz), 4.88(2H,bs).
[0404] To a mixture of tert-butyl [2-(2-hydroxyethoxy)ethyl]carbamate (53.93 g) obtained above and ethyl acetate (350 mL) were added pyridine (53.78 mL) and ethyl chlorocarbonate (70.57 g) under ice-cooling, and the mixture was stirred at room temperature for 96 hrs. Ethyl acetate (500 mL) was added to the reaction mixture, and the mixture was washed with water (500 mL), an aqueous copper sulfate solution (200 mL), water (300 mL) and saturated brine (300 mL) and dried over anhydrous sodium sulfate. Concentration under reduced pressure gave 2-[2-[(tert-butoxycarbonyl) amino]ethoxy]ethyl ethyl carbonate (93.19 g) as a colorless oil.
^{1}H-NMR ($CDCl_3$) : 1.32 (3H,t,J=7.2Hz), 1.44 (9H,s), 3.32 (2H,t, J=5.1Hz), 3.54 (2H,t, J=5.1Hz), 3.67-3.74(2H,m), 4.21 (2H, q, J=7.2Hz), 4.26-4.31(2H,m), 4.91 (1H,bs).
[0405] To a solution (350 mL) of 2-[2-[(tert-butoxycarbonyl)amino]ethoxy]ethyl ethyl carbonate (93.15 g) obtained above and methyl iodide (83.6 mL) in N,N-dimethylformamide was added sodium hydride (60% in oil, 16.12 g) under ice-cooling. After stirring at room temperature for 24 hrs., the reaction mixture was poured into an ice - aqueous ammonium chloride solution, and extracted with diethyl ether (800 mL). The diethyl ether layer was washed with saturated brine (300 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:8). To the purified product was added a 4N hydrogen chloride - ethyl acetate solution (300 mL) was added, and the mixture was stirred at room temperature for 2 hrs. Diethyl ether (300 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (33.21 g) as a white solid.
^{1}H-NMR (DMSO-d_6) : 1.21 (3H,t,J=7.2Hz), 2.51 (3H,s), 3.02-3.09(2H,m), 3.65-3.72 (4H,m), 4. 12 (2H,q,J=7.2Hz), 4.22 (2H,t,J=4.5Hz), 9.06(2H,br).

Reference Example 53

Ethyl 2-[methyl[[2-(methylamino)ethoxy]carbonyl]amino]ethyl carbonate hydrochloride

[0406] To a solution (100 mL) of bis(trichloromethyl)carbonate (11.87 g) in tetrahydrofuran was dropwise added a

solution (20 mL) of pyridine (9.71 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., a solution (20 mL) of tert-butyl 2-hydroxyethyl(methyl)carbamate (17.52 g) obtained in Reference Example 1 in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 15 hrs. After concentration under reduced pressure, water (500 mL) and anhydrous sodium sulfate were added to the residue. After filtration, the filtrate was concentrated under reduced pressure. To the obtained residue were added a solution (50 mL) of 2-(methylamino)ethanol (5.00 g) in ethyl acetate and triethylamine (10.0 mL) under ice-cooling and the mixture was stirred at room temperature for 15 hrs. Ethyl acetate (300 mL) was added to the reaction mixture, the mixture was washed with water (150 mL) and saturated brine (200 mL) and dried over anhydrous sodium sulfate. After concentration under reduced pressure, to a mixture of the residue and ethyl acetate (100 mL) were added pyridine (2.91 mL) and ethyl chlorocarbonate (3.44 g) under ice-cooling, and the mixture was stirred at room temperature for 48 hrs. Ethyl acetate (200 mL) was added to the reaction mixture, the mixture was washed with water (100 mL), an aqueous copper sulfate solution (50 mL), water (50 mL) and saturated brine (50 mL), and dried over anhydrous sodium sulfate. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:3). To the purified product was added a 4N hydrogen chloride - ethyl acetate solution (30 mL), and the mixture was stirred at room temperature for 3 hrs. Diethyl ether (100 mL) was added, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give the title compound (2.90 g) as a white solid.

^{1}H-NMR(DMSO-d_6) : 1.21 (3H,t,J=7.2Hz), 2.57 (3H,bs), 2.86(1.5H,s), 2.93(1.5H,s), 3.16(2H,bs), 3.34 (1H,bs), 3.48 (1H,t,J=5.1Hz), 3.58(1H,t,J=5.1Hz), 4.12(2H,q,J=7.2Hz), 4.16-4.24(4H,m), 8.94 (1H,br).

Reference Example 54

2-(Methylamino)ethyl 1-methylpiperidine-4-carboxylate dihydrochloride

[0407] A mixture of ethyl piperidine-4-carboxylate (4.72 g), methyl iodide (2.24 mL), potassium carbonate (8.29 g) and acetonitrile (50 mL) was stirred at room temperature for 2 hrs. The reaction mixture was concentrated under reduced pressure and water (150 mL) was added. The mixture was extracted with ethyl acetate (150 mL). The ethyl acetate layer was washed with saturated brine (100 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. A 1N aqueous sodium hydroxide solution (20 mL) was added to the residue (2.64 g), and the mixture was stirred overnight at room temperature. The reaction mixture was neutralized by adding 1N hydrochloric acid (20 mL) and the mixture was concentrated under reduced pressure. Ethanol was added to the residue, and the precipitate was filtered off. The filtrate was concentrated under reduced pressure. This step was repeated and ethanol and ethyl acetate were added to the residue for crystallization to give 1-methylpiperidine-4-carboxylic acid (1.79 g) as a colorless solid.

^{1}H-NMR (CD_3OD) : 1.80-1.98 (2H,m), 2.00-2.14 (2H,m), 2.28-2.42 (1H,m), 2.78(3H,s), 2.88-3.04(2H.m), 3.32-3.44 (2H.m).

[0408] A mixture of 1-methylpiperidine-4-carboxylic acid (1.72 g) obtained above, tert-butyl 2-hydroxyethyl(methyl) carbamate (1.75 g) obtained in Reference Example 1, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (2.30 g), 4-dimethylaminopyridine (0.24 g) and acetonitrile (50 mL) was stirred at room temperature for 16 hrs. The reaction mixture was concentrated under reduced pressure and a saturated aqueous sodium hydrogen carbonate solution (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluted with ethyl acetate: hexane=50:50, then 80:20). 1N Hydrochloric acid (25 mL) was added to the purified product (2.73 g), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and isopropanol was added. The mixture was again concentrated under reduced pressure and the precipitated solid was collected by filtration to give the title compound (1.72 g) as a colorless solid.

^{1}H-NMR(DMSO-d_6) : 1.70-2.20 (4H,m), 2.40-3.50 (13H,m), 4.31 (2H,m), 9.25 (2H,br), 10.77 (1H,br).

Reference Example 55

2-[[4-(Aminocarbonyl)phenyl]amino]ethyl acetate

[0409] A mixture of 4-fluorobenzonitrile (6.06 g), 2-aminoethanol (3.71 g), potassium carbonate (8.29 g) and dimethyl sulfoxide (50 mL) was stirred at 100°C overnight. Water (200 mL) was added to the reaction mixture and the mixture was extracted with ethyl acetate (200 mLx4). The ethyl acetate layer was washed with saturated brine (100 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=30:70, then 50:50, then 80:20, then ethyl acetate) to give

4-[(2-hydroxyethyl)amino]benzonitrile (5.89 g) as a yellow solid.
^{1}H-NMR($CDCl_3$) : 2.04 (1H,t,J=4.8Hz), 3.33 (2H,m), 3.86(2H,q,J=4.8Hz), 4.66 (1H,br), 6.58(2H,d,J=8.7Hz), 7.39(2H, d,J=8.7Hz).

[0410] A mixture of 4-[(2-hydroxyethyl)amino]benzonitrile (0.81 g) obtained above, potassium hydroxide (1.12 g) and tert-butanol (20 mL) was stirred at 100°C for 1 hr. Water (100 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (80 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To a solution (10 mL) of the residue (0.83 g), pyridine (0.49 mL) and 4-dimethylaminopyridine (0.061 g) in tetrahydrofuran was dropwise added a solution (1 mL) of acetic anhydride (0.57 mL) in tetrahydrofuran. The mixture was stirred at room temperature for 1 hr., water (80 mL) was added, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (80 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=30:70, then 60:40) to give the title compound (0.68 g) as a colorless solid.
^{1}H-NMR($CDCl_3$) : 2.08 (3H,s), 3.44 (2H,q,J=5.6Hz), 4.29 (2H,t,J=5.4Hz), 4.48 (1H,br), 6.59 (2H,d,J=8.9Hz), 7.43(2H, d,J=8.9Hz).

Reference Example 56

2-(Methylamino)ethyl 1-methyl-4-piperidinyl carbonate dihydrochloride

[0411] To a solution (40 mL) of N,N'-carbonyldiimidazole (3.36 g) in tetrahydrofuran was dropwise added slowly a solution (10 mL) of tert-butyl 2-hydroxyethyl(methyl)carbamate (3.30 g) obtained in Reference Example 1 in'tetrahydrofuran under ice-cooling. The mixture was stirred under ice-cooling for 40 min. and at room temperature for 2 hrs. N,N'-Carbonyldiimidazole (0.31 g) was added and the mixture was further stirred for 3 days. The reaction mixture was concentrated under reduced pressure and ethyl acetate (150 mL) was added to the residue. The mixture was washed with saturated brine (100 mL×2), water (50 mLx3) and saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 2-[(tert-butoxycarbonyl)(methyl)amino]ethyl 1H-imidazole-1-carboxylate (5.24 g) as a colorless oil.
^{1}H-NMR ($CDCl_3$) : 1.39 (9H×0.5,s), 1.42 (9H×0.5,s), 2.94 (3H,m), 3.63 (2H,m), 4.51 (2H,t,J=5.3Hz), 7.06 (1H,m), 7.42 (1H,m), 8.13 (1H,s).

[0412] A mixture of 2-[(tert-butoxycarbonyl)(methyl)amino]ethyl 1H-imidazole-1-carboxylate (1.35 g) obtained above, 1-methyl-4-piperidinol (1.38 g) and acetonitrile (20 mL) was stirred overnight at room temperature. 1-Methyl-4-piperidinol (0.92 g) was added and the mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure and a saturated aqueous sodium hydrogen carbonate solution (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 1N Hydrochloric acid (12 mL) was added to the residue (1.60 g), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, water, isopropanol and ethyl acetate were added, and the precipitated solid was collected by filtration to give the title compound (1.09 g) as a colorless solid.
^{1}H-NMR(DMSO-d_6) : 1.85-2.20 (4H,m), 2.55 (3H,s), 2.70(3H×0.5,s), 2.73 (3H×0.5,s), 2.90-3.50 (6H,m), 4.38 (2H,m), 4.65-5.00 (1H,m), 9.21 (2H,br), 11.10(1H,br).

Synthetic Example 1

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl acetate

[0413] To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl acetate hydrochloride (0.77 g) obtained in Reference Example 2 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The mixture was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60°C overnight. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over

anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate), and further by silica gel column chromatography (eluted with ethyl acetate:hexane=2:1, then ethyl acetate, then acetone:ethyl acetate=1:4, then 1:1) to give the title compound (1.13 g) as a yellow amorphous solid.
^{1}H-NMR($CDCl_3$) : 2.10(3H,s), 2.24(3H,s), 3.09(3H,bs), 3.60-4.00(2H,br), 4.25-4.50 (4H,m), 4. 89 (1H,d,J=13.3Hz), 5.05 (1H,d,J=13.3Hz), 6.65 (1H,d,J=5.5Hz), 7.35-7.51(3H,m), 7.80-7.90 (1H,m), 8.35 (1H,d,J=5.5Hz).

Synthetic Example 2

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl trimethylacetate

[0414] To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., 2-(methylamino)ethyl trimethylacetate hydrochloride (0.98 g) obtained in Reference Example 3 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred overnight at room temperature. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred overnight at 60°C. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:3, then 3:2). Crystallization from acetone-diisopropyl ether and recrystallization from acetone-diisopropyl ether gave the title compound (1.01 g) as a colorless solid.
^{1}H-NMR ($CDCl_3$) : 1.23 (9H,s), 2.23(3H,s), 3.08(3H,bs), 3.40-4. 30 (2H,br), 4. 30-4. 50 (4H,m), 4. 80-5. 20 (2H,br), 6.64 (1H,d,J=5.7Hz), 7.35-7.50 (3H,m), 7.78-7. 88 (1H,m), 8.35(1H,d,J=5.7Hz).

Synthetic Example 3

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl cyclohexanecarboxylate

[0415] To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl cyclohexanecarboxylate hydrochloride (1.11 g) obtained in Reference Example 4 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred overnight at 60°C. After concentration under reduced pressure, water (50 mL) was added to the residue.
The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:3, then 3:2). Crystallization from acetone-diisopropyl ether and recrystallization from acetone-diisopropyl ether gave the title compound (1.11 g) as a colorless solid.
^{1}H-NMR ($CDCl_3$) : 1.10-1. 55 (5H,m), 1.55-1.82 (3H,m), 1.84-1.98(2H,m), 2.23(3H,s), 2.27-2.40(1H,m), 3.08(3H,bs), 3.40-4.30(2H,br), 4.30-4.50(4H,m), 4.80-5.15(2H,br), 6.64(1H,d,J=5.4Hz), 7.35-7.48(3H,m), 7.84(1H,d,J=6.9Hz), 8.34 (1H,d,J=5.4Hz).

Synthetic Example 4

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl benzoate

[0416] To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., 2-(methylamino)ethyl benzoate hydrochloride (1.08 g) obtained in Reference Example 5 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred overnight at room temperature. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred overnight at 60°C. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:3, then 3:2). Crystallization from acetone-diethyl ether and recrystallization from acetone-diethyl ether gave the title compound (1.09 g) as a colorless solid.
^{1}H-NMR($CDCl_3$): 2.22 (3H,s), 3.12 (3H,bs), 3.50-4.30 (2H,br), 4.37 (2H, q, J=7. 8Hz), 4.68 (2H,m), 4.80-5.20 (2H,br), 6.63(1H,d,J=5.7Hz), 7.26-7.48(5H,m), 7.53-7.61(1H,m), 7.82(1H,d,J=8.1Hz), 8.04(2H,d,J=7.2Hz), 8.33(1H,d, J=5.7Hz).

Synthetic Example 5

2-[Methyl[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl benzoate

[0417] To a solution (30 mL) of bis(trichloromethyl)carbonate (0.99 g) in tetrahydrofuran was dropwise added a solution (2 mL) of pyridine (0.81 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl benzoate hydrochloride (2.16 g) obtained in Reference Example 5 was added. After addition of a solution (2 mL) of triethylamine (1.39 mL) in tetrahydrofuran, the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, ethyl acetate (100 mL) and water (100 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (40 mL). 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (2.90 g), triethylamine (2.20 mL) and 4-dimethylaminopyridine (0.096 g) were added, and the mixture was stirred at 60°C for 2 hr. After concentration under reduced pressure, ethyl acetate (150 mL) and water (80 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate). Recrystallization from acetone gave the title compound (2.62 g) as a colorless solid.
^{1}H-NMR($CDCl_3$) : 2.22 (3H,s), 3.13 (3H,bs), 3.68-3.98 (2H,m), 4.38 (2H,q,J=7.8Hz), 4.69 (2H,m), 4.80-5.10(2H,bm), 6.64 (1H, d, J=5.7Hz), 7.27-7.48 (5H,m), 7.59 (1H,m), 7.83 (1H,m), 8.06(2H, d, J=6.0Hz), 8.35(1H, d, J=5.7Hz).

Synthetic Example 6

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl 4-methoxybenzoate

[0418] To a solution (18 mL) of bis(trichloromethyl)carbonate (0.584 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 40 min., 2-(methylamino)ethyl 4-methoxybenzoate hydrochloride (1.48 g) obtained in Reference Example 6 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at room temperature for 80 min. After concentration under reduced pressure, ethyl acetate (80 mL) and water (50 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (25 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimi-

dazole (1.55 g), triethylamine (1.17 mL) and 4-dimethylaminopyridine (0.051 g) were added, and the mixture was stirred at 60°C for 3 hrs. After concentration under reduced pressure, ethyl acetate (150 mL) and water (50 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate). Recrystallization from ethyl acetate-hexane gave the title compound (1.08 g) as a colorless solid.
^{1}H-NMR($CDCl_3$): 2.22(3H,s), 3.11(3H,bs), 3.68-3.90(2H,bm), 3.85 (3H,s), 4.37(2H,q,J=7.9Hz), 4.58-4.72 (2H,m), 4.82-5.14(2H,bm), 6.63 (1H,d,J=5.7Hz), 6.91 (2H,d,J=9.0Hz), 7.27-7.40 (3H,m), 7.82 (1H,m), 7.99 (2H,d,J=9.0Hz), 8.33(1H,d,J=5.7Hz).

Synthetic Example 7

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl 3-chlorobenzoate

[0419] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl 3-chlorobenzoate hydrochloride (1.50 g) obtained in Reference Example 7 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (40 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (25 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.44 g), triethylamine (1.09 mL) and 4-dimethylaminopyridine (0.048 g) were added, and the mixture was stirred at 60°C for 3 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (40 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (0.84 g) as colorless syrup.
^{1}H-NMR($CDCl_3$) : 2.21(3H,s), 3.12 (3H,bs), 3.78-4.08 (2H,bm), 4.38 (2H,q,J=7.8Hz), 4.64-5.08(4H,bm), 6.64 (1H,d, J=5.2Hz), 7.34-7.42 (4H,m), 7.56 (1H,m), 7.82 (1H,m), 7.94 (1H,d,J=7.6Hz), 8.02 (1H,s), 8.34 (1H,d,J=5.2Hz).

Synthetic Example 8

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl 3,4-difluorobenzoate

[0420] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl 3,4-difluorobenzoate hydrochloride (1.51 g) obtained in Reference Example 8 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (50 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (25 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.71 g), triethylamine (1.29 mL) and 4-dimethylaminopyridine (0.056 g) were added, and the mixture was stirred at 60°C for 17 hrs. After concentration under reduced pressure, ethyl acetate (100 mL) and water (50 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, and the aqueous layer was extracted with ethyl acetate (20 mL). Ethyl acetate layers were combined, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then 2:1), and further by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1). Crystallization from acetone-diisopropyl ether and recrystallization from ethyl acetate-hexane gave the title compound (1.37 g) as a colorless solid.
^{1}H-NMR ($CDCl_3$) : 2.21 (3H, s), 3.11 (3H,bs), 3.82-4.08 (2H,bm), 4.38(2H,q,J=7.8Hz), 4.60-5.14(4H,bm), 6.63 (1H,d, J=5.7Hz), 7.20 (1H,m), 7.33-7.41 (3H,m), 7.78-7.92 (3H,m), 8.33 (1H,d,J=5.7Hz).

Synthetic Example 9

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl 4-trifluoromethoxybenzoate

[0421] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl 4-trifluoromethoxybenzoate hydrochloride (1.79 g) obtained in Reference Example 9 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at room temperature for 1.5 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (50 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (25 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.57 g), triethylamine (1.18 mL) and 4-dimethylaminopyridine (0.052 g) were added, and the mixture was stirred at 60°C for 4.5 hrs. After concentration under reduced pressure, ethyl acetate (100 mL) and water (50 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, and the aqueous layer was extracted with ethyl acetate (30 mL). The ethyl acetate layers were combined, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1), and further by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1) to give the title compound (1.44 g) as colorless syrup.
^{1}H-NMR ($CDCl_3$) : 2.22 (3H,s), 3.11 (3H,bs), 3.85-4.05 (2H,bm), 4.38(2H,q,J=7.8Hz), 4.60-5.12 (4H,bm), 6.64 (1H,d, J=5.7Hz), 7.24 (2H,d,J=8.7Hz), 7.25-7.40 (3H,m), 7.82 (1H,d,J=7.2Hz), 8.09 (2H,d,J=8.7Hz), 8.33 (1H,d,J=5.7Hz).

Synthetic Example 10

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl 4-fluorobenzoate

[0422] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl 4-fluorobenzoate hydrochloride (1.40 g) obtained in Reference Example 10 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (40 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.32 g), triethylamine (1.00 mL) and 4-dimethylaminopyridine (0.049 g) were added, and the mixture was stirred at 60°C for 14.5 hrs. After concentration under reduced pressure, ethyl acetate (150 mL) and water (50 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was crystallized from ethyl acetate:hexane=1:1 and the solid was collected by filtration. Recrystallization from acetone gave the title compound (1.39 g) as a colorless solid.
^{1}H-NMR($CDCl_3$) : 2.22 (3H,s), 3.12(3H,bs), 3.78-4.20 (2H,bm), 4.38(2H,q,J=7.8Hz), 4.58-5.08(4H,bm), 6.65(1H,d, J=5.6Hz), 7.11(2H,t,J=8.4Hz), 7.28-7.44(3H,m), 7.81-7.86(1H,m), 8.03-8.11(2H,m), 8.35 (1H,d,J=5.6Hz).

Synthetic Example 11

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl 3,4,5-trimethoxybenzoate

[0423] To a solution (30 mL) of bis(trichloromethyl)carbonate (0.60g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 10 min., 2-(methylamino)ethyl 3,4,5-teimethoxybenzoate hydrochloride (1.22 g) obtained in Reference Example 11 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with dilute hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyri-

dyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60°C for 3 hrs. and at room temperature for 2 days. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:3, then 3:2) to give the title compound (1.56 g) as a yellow amorphous solid.
^{1}H-NMR($CDCl_3$) : 2.21 (3H,s), 3.12(3H,bs), 3.50-4.30 (2H,br), 3.83(6H,s), 3.90(3H,s), 4.38(2H,q,J=7.8Hz), 4.67 (2H, m), 4.80-5.15(2H,br), 6.64(1H,d,J=5.7Hz), 7.25-7.40(5H,m), 7.78-7.86(1H,m), 8.33 (1H,d,J=5.7Hz).

Synthetic Example 12

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl 2-pyridinecarboxylate

[0424] To a solution (30 mL) of bis(trichloromethyl)carbonate (0.422 g) in tetrahydrofuran was dropwise added pyridine (0.345 mL) under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl 2-pyridinecarboxylate dihydrochloride (1.08 g) obtained in Reference Example 12 was added. After dropwise addition of triethylamine (1.19 mL), the mixture was stirred at room temperature for 2 hrs. The precipitated solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (10 mL), and (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.31 g), triethylamine (0.99 mL) and 4-dimethylaminopyridine (0.043 g) were added. The mixture was stirred at 60°C for 24 hrs. Ethyl acetate (100 mL) was added to the reaction mixture, and the mixture was washed with water (100 mL) and saturated brine (100 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=4:1). Crystallization from acetone-diethyl ether gave the title compound (0.9 g) as a white solid.
^{1}H-NMR($CDCl_3$) : 2.22 (3H,s), 3.16 (3H,s), 3.80-4.20 (2H,m), 4.38 (2H,q,J=7.8Hz), 4.60-5.10(4H,m), 6.64 (1H,d, J=5.8Hz), 7.29-7.40(2H,m), 7.47-7.52 (2H,m), 7.81-7.89(2H,m), 8.14(1H,d,J=7.8Hz), 8.34(1H,d,J=5.8Hz), 8.75-8.79 (1H,m).

Synthetic Example 13

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl methoxyacetate

[0425] To a solution (15 mL) of bis(trichloromethyl)carbonate (0.652 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.55 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl methoxyacetate (0.99 g) obtained in Reference Example 13 was added. The mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (50 mL) were added to the residue and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (15 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.13 g), triethylamine (0.86 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60°C for 4 days. After concentration under reduced pressure, ethyl acetate (80 mL) and water (30 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, and the ethyl acetate layer was washed with a saturated aqueous sodium hydrogen carbonate solution (30 mL) and water (30 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate, then acetone:ethyl acetate=1:3), and further by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then 3:1) to give the title compound (0.588 g) as colorless syrup.
^{1}H-NMR($CDCl_3$) : 2.32 (3H,s), 2.68 (3H,s), 3.48 (3H,s), 3.69-4.02(4H,m), 4.38(2H,q,J=7.8Hz), 4.67 (2H,t,J=6.6Hz), 4.99 (1H,d,J=13.9Hz), 5.12 (1H,d,J=13.9Hz), 6.63 (1H,d,J=5.7Hz), 7.29-7.46 (2H,m), 7.62 (1H,m), 7.81 (1H,m), 8.25 (1H,d,J=5.7Hz).

Synthetic Example 14

Ethyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate

[0426] To a solution (40 mL) of bis(trichloromethyl)carbonate (1.31 g) in tetrahydrofuran was dropwise added a solution (2 mL) of pyridine (1.07 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 10 min., ethyl 2-(methylamino)ethyl carbonate hydrochloride (2.02 g) obtained in Reference Example 14 was added. A solution (2 mL) of triethylamine (1.84 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (100 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (50 mL) and saturated brine (100 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (50 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (3.69 g), triethylamine (2.09 mL) and 4-dimethylaminopyridine (0.12 g) were added, and the mixture was stirred at 60°C for 6 hrs. and at room temperature for 8 hrs. After concentration under reduced pressure, water (100 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate: hexane=3:7, then ethyl acetate). Crystallization from diethyl ether and recrystallization from diethyl ether gave the title compound (3.84 g) as a colorless solid.
^{1}H-NMR($CDCl_3$) : 1.32(3H,t,J=7.2Hz), 2.23(3H,s), 3.10(3H,bs), 3.50-4.20 (2H,br), 4.22 (2H,q,J=7.2Hz), 4.39 (2H,q, J=7.9Hz), 4.45(2H,m), 4.80-5.15(2H,br), 6.65(1H,d,J=5.6Hz), 7.36-7.50(3H,m), 7. 84 (1H,d,J=7. 8Hz), 8.35 (1H,d, J=5.6Hz).

Synthetic Example 15

Isopropyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate

[0427] To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., isopropyl 2-(methylamino)ethyl carbonate hydrochloride (0.99 g) obtained in Reference Example 15 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. Bis(trichloromethyl)carbonate (0.50 g), a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran and a solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran were successively added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60°C for 12 hrs. and at room temperature for 3 days. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:3, then 3:2), and further by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then ethyl acetate). Crystallization from diethyl ether and recrystallization from acetone-diisopropyl ether gave the title compound (0.58 g) as a colorless solid.
^{1}H-NMR($CDCl_3$) : 1.31 (6H,d,J=6.3Hz), 2.23 (3H,s), 3.08 (3H,bs), 3.40-4.30(2H,br), 4.37(2H,q,J=7.9Hz), 4.32-4.53 (2H,m), 4.80-5.20(3H,m), 6.63(1H,d,J=5.7Hz), 7.35-7.50(3H,m), 7.83(1H,d,J=7.2Hz), 8.34(1H,d,J=5.7Hz).

Synthetic Example 16

Isopropyl 2-[methyl[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate

[0428] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., isopropyl 2-(methylamino)ethyl carbonate hydrochloride (1.18 g) obtained in Reference Example 15 was added. A

solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was added and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, ethyl acetate (80 mL) and water (30 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (25 mL). 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.73 g), triethylamine (1.31 mL) and 4-dimethylaminopyridine (0.057 g) were added, and the mixture was stirred at 60°C for 5 hrs. After concentration under reduced pressure, ethyl acetate (100 mL) and water (50 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1), and further by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then 2:1). Crystallization from diisopropyl ether-hexane and recrystallization from diisopropyl ether gave the title compound (1.20 g) as a colorless solid.
^{1}H-NMR($CDCl_3$) : 1.31(6H,d,J=6.6Hz), 2.23(3H,s), 3.08(3H,bs), 3.50-3.90(2H,bm), 4.38(2H,q,J=7.8Hz), 4.36-4.58 (2H,bm), 4.79-5.15 (3H,m), 6.64 (1H,d,J=5.7Hz), 7.35-7.48 (3H,m), 7.83(1H,d,J=7.5Hz), 8.34(1H,d,J=5.7Hz).

Synthetic Example 17

Benzyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate

[0429] To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., benzyl 2-(methylamino)ethyl carbonate hydrochloride (1.08 g) obtained in Reference Example 16 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred overnight at room temperature. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred overnight at 60°C. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:3, then 3:2). Crystallization from acetone-diethyl ether and recrystallization from acetone-diethyl ether gave the title compound (1.17 g) as a colorless solid.
^{1}H-NMR($CDCl_3$) : 2.22 (3H,s), 3.05 (3H,bs), 3.50-4.20 (2H,br), 4.37(2H,q,J=7.8Hz), 4.46(2H,m), 4.80-5.10 (2H,br), 5.17(2H,s), 6.62(1H,d,J=5.6Hz), 7.26-7.48(8H,m), 7.77-7.88(1H,m), 8.33(1H,d,J=5.6Hz).

Synthetic Example 18

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl tetrahydropyran-4-yl carbonate

[0430] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.48 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.39 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 20 min., 2-(methylamino)ethyl tetrahydropyran-4-yl carbonate hydrochloride (0.96 g) obtained in Reference Example 17 was added. A solution (1 mL) of triethylamine (0.67 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.26 g), triethylamine (0.71 mL) and 4-dimethylaminopyridine (0.042 g) were added, and the mixture was stirred at 60°C for 6 hrs. and at room temperature for 8 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then ethyl acetate). Crystallization from diethyl ether and recrystallization from acetone-diisopropyl ether gave the title compound (1.45 g) as a colorless solid.
^{1}H-NMR ($CDCl_3$) : 1.64-1.81 (2H,m), 1.92-2.03 (2H,m), 2.23 (3H,s), 3.09(3H,bs), 3.40-4.30 (2H,br), 3.45-3.57 (2H,m),

3.87-3.97 (2H,m), 4.38 (2H,q,J=7.8Hz), 4.45(2H,m), 4.77-5.15(3H,m), 6.64 (1H,d,J=5.7Hz), 7.35-7.50(3H,m), 7.83 (1H,d,J=6.9Hz), 8.35 (1H,d,J=5.7Hz).

Synthetic Example 19

2-Methoxyethyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl] carbonyl]amino]ethyl carbonate

[0431] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 10 min., 2-methoxyethyl 2-(methylamino)ethyl carbonate hydrochloride (1.07 g) obtained in Reference Example 18 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.85 g), triethylamine (1.05 mL) and 4-dimethylaminopyridine (0.061 g) were added, and the mixture was stirred at 60°C for 6 hrs. and at room temperature for 8 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then ethyl acetate). Crystallization from ethyl acetate-diethyl ether and recrystallization from ethyl acetate-diisopropyl ether gave the title compound (1.39 g) as a colorless solid.
^{1}H-NMR($CDCl_3$): 2.23(3H,s), 3.09(3H,bs), 3.37 (3H,s), 3.50-4.20(2H,br), 3.59-3.65(2H,m), 4.28-4.33(2H,m), 4.38(2H, q,J=7.8Hz), 4.46 (2H,m), 4.80-5.15(2H,br), 6. 64 (1H,d,J=5. 7Hz), 7.35-7.47 (3H,m), 7. 83 (1H,d,J=7. 8Hz), 8.34(1H, d,J=5.7Hz).

Synthetic Example 20

2-[Ethyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl acetate

[0432] To a solution (30 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 10 min., 2-(ethylamino)ethyl acetate hydrochloride (0.67 g) obtained in Reference Example 20 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred overnight at 60°C. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then ethyl acetate) to give the title compound (1.58 g) as a yellow amorphous solid.
^{1}H-NMR ($CDCl_3$) : 1.25 (3H,m), 2.08 (3H,s), 2.23 (3H,s), 3.30-4.10(4H,br), 4.23-4.45(2H,m), 4.38 (2H,q,J=7.8Hz), 4.75-5.20 (2H,br), 6.64 (1H,d,J=5.7Hz), 7.35-7.46 (3H,m), 7.84(1H,d,J=6.9Hz), 8.36(1H,d,J=5.7Hz).

Synthetic Example 21

2-[Isopropyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl] amino]ethyl acetate

[0433] To a solution (10 mL) of bis(trichloromethyl)carbonate (0.543 g) in tetrahydrofuran was dropwise added a solution (5 mL) of pyridine (0.445 mL) in tetrahydrofuran under ice-cooling, and the mixture was stirred at 0°C for 30 min. 2-(Isopropylamino)ethyl acetate hydrochloride (1.0 g) obtained in Reference Example 22 was added to the reaction mixture. A solution (5 mL) of triethylamine (0.805 mL) in tetrahydrofuran was added, and the mixture was stirred at

room temperature for 30 min. The reaction mixture was concentrated under reduced pressure, water (30 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained oil was dissolved in tetrahydrofuran (5 mL), and added to a solution (20 mL) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.73 g), triethylamine (1.53 mL) and 4-dimethylaminopyridine (0.134 g) in tetrahydrofuran. The mixture was stirred at 40°C for 12 hrs. The reaction mixture was concentrated under reduced pressure and water (30 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=2:1, then ethyl acetate) to give the title compound (1.50 g) as a pale-yellow amorphous solid.
^{1}H-NMR($CDCl_3$) : 1.20-1.40 (6H,m), 2.05 (3H×0.4,s), 2.11 (3H×0.6,s), 2.18 (3H×0.6,s), 2.27 (3H×0.4,s), 3.40-3.60 (1H,m), 3.70-4.60 (6H,m), 4.70-5.25 (2H,m), 6.65 (1H,d,J=5.8Hz), 7.30-7.50(3H,m), 7.75-7.90(1H,m), 8.37 (1H,d, J=5.8Hz).

Synthetic Example 22

Ethyl 2-[isopropyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl] amino]ethyl carbonate

[0434] To a solution (10 mL) of bis(trichloromethyl)carbonate (0.467 g) in tetrahydrofuran was dropwise added a solution (5 mL) of pyridine (0.381 mL) in tetrahydrofuran under ice-cooling, and the mixture was stirred at 0°C for 30 min. Ethyl 2-(isopropylamino)ethyl carbonate hydrochloride (1.0 g) obtained in Reference Example 23 was added to the reaction mixture. A solution (5 mL) of triethylamine (0.69 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at 0°C for 15 min. and at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure and water (30 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained oil was dissolved in tetrahydrofuran (5 mL), and added to a solution (20 mL) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.48 g), triethylamine (1.32 mL) and 4-dimethylaminopyridine (0.115 g) in tetrahydrofuran, and the mixture was stirred at 40°C for 12 hrs. The reaction mixture was concentrated under reduced pressure and water (30 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=2:1, then ethyl acetate) to give the title compound (1.20 g) as a pale-yellow amorphous solid.
^{1}H-NMR ($CDCl_3$) : 1.20-1.40 (9H,m), 2.17 (3H×0. 6,s), 2.27(3H×0.4,s), 3.40-3.70(1H,m), 3.75-4.65(8H,m), 4.70-5.30 (2H,m), 6.64(1H,d,J=5.8Hz), 7.35-7.55(3H,m), 7.75-7.90(1H,m), 8.38(1H,d,J=5.8Hz).

Synthetic Example 23

2-[Cyclohexyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl] amino]ethyl acetate

[0435] To a solution (10 mL) of bis(trichloromethyl)carbonate (0.593 g) in tetrahydrofuran was dropwise added pyridine (0.485 mL) under ice-cooling. After stirring under ice-cooling for 30 min., 2-(cyclohexylamino)ethyl acetate hydrochloride (1.33 g) obtained in Reference Example 25 was added. Triethylamine (0.84 mL) was dropwise added, and the mixture was stirred at room temperature for 2 hrs. Ethyl acetate (50 mL) was added to the reaction mixture and the mixture was washed with water (50 mL) and saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), and (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.61 g), triethylamine (1.21 mL) and 4-dimethylaminopyridine (0.053 g) were added. The mixture was stirred at 60°C for 24 hrs. Ethyl acetate (50 mL) was added to the reaction mixture, and the mixture was washed with water (20 mL) and saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (eluted with ethyl acetate:hexane=1:4, then ethyl acetate) to give the title compound (2.12 g) as a pale-yellow amorphous solid. ^{1}H-NMR($CDCl_3$): 1.00-2.42(16H,m), 3.30-3.70 (2H,m), 3.80-4.00(1H,m), 4.27-4.42(2H,m), 4.40(2H,q,J=8.2Hz), 4.78(1H×0.5,d,J=13.2Hz), 4.97(2H×0.5,s), 5.20(1H×0.5,d,J=13.2Hz), 6.67(1H,d,J=5.8Hz), 7.36-7.46(3H,m), 7.81-7.91(1H,m), 8.39 (1H,d,J=5.8Hz).

Synthetic Example 24

2-[Cyclohexyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl] amino]ethyl ethyl carbonate

[0436] To a solution (10 mL) of bis(trichloromethyl)carbonate (0.238 g) in tetrahydrofuran was dropwise added pyridine (0.20 mL) under ice-cooling. After stirring under ice-cooling for 30 min., 2-(cyclohexylamino)ethyl ethyl carbonate hydrochloride (0.605 g) obtained in Reference Example 26 was added. Triethylamine (0.335 mL) was dropwise added, and the mixture was stirred at room temperature for 2 hrs. Ethyl acetate (50 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL) and saturated brine (50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (10 mL), and (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.60 g), triethylamine (0.45 mL) and 4-dimethylaminopyridine (0.02 g) were added. The mixture was stirred at 60°C for 24 hrs. Ethyl acetate (50 mL) was added to the reaction mixture, and the mixture was washed with water (20 mL) and saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (eluted with ethyl acetate:hexane=1:4, then ethyl acetate) to give the title compound (0.92 g) as a pale-yellow amorphous solid.
^{1}H-NMR($CDCl_3$) : 1.02-2.27 (16H,m), 3.40-4.60 (9H,m), 4.78 (1H×0.5,d,J=13.2Hz), 4.97 (2H×0.5,s), 5.44 (1H×0.5,d, J=13.2Hz), 6.69 (1H,d,J=5.6Hz), 7.32-7.54(3H,m), 7.80-7.91 (1H,m), 8.38 (1H,d,J= 5.6Hz).

Synthetic Example 25

2-[[[(R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](phenyl) amino]ethyl acetate

[0437] To a solution (350 mL) of bis(trichloromethyl)carbonate (13.4 g) in tetrahydrofuran was dropwise added pyridine (10.38 mL) under ice-cooling. After stirring under ice-cooling for 30 min., 2-anilinoethyl acetate hydrochloride (25.9 g) obtained in Reference Example 27 was added. Triethylamine (18.4 mL) was dropwise added, and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, ethyl acetate (500 mL) and water (500 mL) were added to the residue, and the mixture was stirred. The ethyl acetate layer was separated and taken, washed with saturated brine (500 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 2-[(chlorocarbonyl)(phenyl)amino]ethyl acetate. This was dissolved in tetrahydrofuran (300 mL), (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (41.2 g), triethylamine (15.6 mL) and 4-dimethylaminopyridine (1.363 g) were added, and the mixture was stirred at 60°C for 3 hrs. Ethyl acetate (800 mL) was added to the reaction mixture, and the mixture was washed twice with water (800 mL) and with saturated brine (800 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then 1:1). Crystallization from diethyl ether gave the title compound (54.1 g) as a white solid.
^{1}H-NMR ($CDCl_3$) : 2.00(3H,s), 2.25(3H,s), 4.15-4.48(6H,m), 4.83(1H,d,J=13.6Hz), 5.05(1H,d,J=13.6Hz), 6.67(1H,d, J=5.4Hz), 7.03-7.45(8H,m), 7.64-7.69(1H,m), 8.40(1H,d,J=5.4Hz).

Synthetic Example 26

2-[[[2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](phenyl)amino] ethyl acetate

[0438] To a solution (10 mL) of 2-[(chlorocarbonyl)(phenyl)amino]ethyl acetate (0.58 g) prepared in the same manner as in Synthetic Example 25 in tetrahydrofuran were added 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.739 g), triethylamine (0.558 mL) and 4-dimethylaminopyridine (0.024 g), and the mixture was stirred at 60°C for 15 hrs. Ethyl acetate (30 mL) was added to the reaction mixture, and the mixture was washed with water (50 mL) and saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:4, then 3:2). Crystallization from diethyl ether gave the title compound (0.779 g) as a white solid.
^{1}H-NMR($CDCl_3$) : 1.99 (3H,s), 2.25 (3H,s), 4.20-4.48 (6H,m), 4.83(1H,d,J=13.6Hz), 5.05(1H,d,J=13.6Hz), 6.67(1H,d, J=5.8Hz), 7.03-7.45(8H,m), 7.64-7.69(1H,m), 8.40(1H,d,J=5.8Hz).

Synthetic Example 27

tert-Butyl [2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]-3-pyridyl]methyl carbonate

[0439] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.30 g) in tetrahydrofuran was dropwise added pyridine (0.24 mL) under ice-cooling. After stirring under ice-cooling for 30 min., tert-butyl [2-(methylamino)-3-pyridyl]methyl carbonate (0.71 g) obtained in Reference Example 28 was added, and the mixture was stirred at room temperature for 2 hrs. The precipitated solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL), (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.92 g), triethylamine (0.70 mL) and 4-dimethylaminopyridine (0.031 g) were added, and the mixture was stirred at 60°C for 1 hr. Water (50 mL) was added to the reaction mixture and the mixture was extracted twice with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:2), and further by basic silica gel column chromatography (eluted with ethyl acetate) to give the title compound (0.38 g) as a pale-yellow amorphous solid.
^{1}H-NMR($CDCl_3$) : 1.46(9H,s), 2.25 (3H,s), 3.54 (3H,s), 4.37(2H,q,J=8.0Hz), 4.95(2H,s), 5.15(1H,d,J=14.0Hz), 5.27 (1H,d,J=14.0Hz), 6.63(1H,d,J=5.4Hz), 7.26-7.45(3H,m), 7.69-7.87(3H,m), 8.33(1H,d,J=5.4Hz), 8.44-8.46(1H,m).

Synthetic Example 28

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]benzyl acetate

[0440] To a solution (30 mL) of bis(trichloromethyl)carbonate (1.46 g) in tetrahydrofuran was dropwise added pyridine (1.16 mL) under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)benzyl acetate (2.57 g) obtained in Reference Example 29 was added. The mixture was stirred at room temperature for 3 hrs. The precipitated solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (40 mL), (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (4.41 g), triethylamine (3.33 mL) and 4-dimethylaminopyridine (0.15 g) were added, and the mixture was stirred at 60°C for 18 hrs. Water (100 mL) was added to the reaction mixture, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (100 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (eluted with acetone:hexane=1:4, then 1:2). Crystallization from ethyl acetate-diethyl ether-hexane gave the title compound (2.76 g) as a while solid.
^{1}H-NMR($CDCl_3$) : 2.10 (3H,s), 2.00-2.30 (3H,br), 3.20-3.50 (3H,br), 4.38(2H,q,J=7.6Hz), 4.70-5.20(2H,m), 5.20-5.50 (2H,m), 6.65(1H,d,J=5.4Hz), 7.10-7.82(BH,m), 8.38(1H,d,J=5.4Hz).

Synthetic Example 29

2-[[2-(Acetyloxy)ethyl][[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate

[0441] To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 10 min., 2-[(2-acetyloxyethyl)amino]ethyl acetate hydrochloride (1.13 g) obtained in Reference Example 30 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. The precipitated solid was filtered off and the filtrate was concentrated under reduced pressure. Ethyl acetate (20 mL) was added to the residue, the precipitated solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (30 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.48 g), triethylamine (1.12 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60°C overnight. After concentration under reduced pressure, water (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate), and further by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate). The resulting product was dissolved in ethyl acetate (20 mL), activated carbon was added and the mixture was stirred overnight. The activated carbon was filtered off and the filtrate was concentrated under reduced

pressure to give the title compound (1.60 g) as a yellow amorphous solid.
^{1}H-NMR ($CDCl_3$) : 2.06(3H,s), 2.08(3H,s), 2.24(3H,s), 3.40-4.45(8H,m), 4.39(2H,q,J=7.9Hz), 4.88 (1H,d,J=13.2Hz), 5.05 (1H,d,J=13.2Hz), 6.66 (1H,d,J=5.6Hz), 7.38-7.50(3H,m), 7.87(1H,d,J=6.9Hz), 8.36 (1H,d,J=5.6Hz).

Synthetic Example 30

[(2S)-1-[[(R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]-2-pyrrolidinyl]methyl acetate

[0442] To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., (S)-2-pyrrolidinylmethyl acetate hydrochloride (0.90 g) obtained in Reference Example 31 was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.84 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60°C for 1 day and at room temperature for 2 days. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate) and further by silica gel column chromatography (eluted with ethyl acetate:hexane=3:1, then ethyl acetate, then acetone:ethyl acetate=1:4, then 2:3) to give the title compound (0.80 g) as a pale-yellow amorphous solid.
^{1}H-NMR ($CDCl_3$) : 1.80-2.30 (4H,m), 2.09(3H,s), 2.30(3H,s), 3.39(1H,m), 3.50-3.62(1H,m), 4.20-4.45 (4H,m), 4.58(1H,m), 4.89(1H,d,J=13.5Hz), 4.96(1H,d,J=13.5Hz), 6.65(1H,d,J=5.9Hz), 7.36-7.48(3H,m), 7.89(1H,d,J=8.7Hz), 8.38(1H,d,J=5.9Hz).

Synthetic Example 31

Ethyl [methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]acetate

[0443] To a solution (30 mL) of bis(trichloromethyl)carbonate (0.50 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.40 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., sarcosine ethyl ester hydrochloride (0.77 g) was added. A solution (1 mL) of triethylamine (0.70 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. The precipitated solid was filtered off and the filtrate was concentrated under reduced pressure. Water (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (33 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole sodium salt (1.37 g) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60°C overnight. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate) to give the title compound (0.40 g) as a yellow amorphous solid.
^{1}H-NMR($CDCl_3$) : 1.33 (3H,t,J=7.1Hz), 2.24 (3H,s), 3.10 (3H,bs), 3.70-4.30(2H,br), 4.28 (2H,q,J=7.1Hz), 4.38 (2H,q,J=7.8Hz), 4.82-5.10(2H,br), 6.63 (1H,d,J=5.5Hz), 7.34-7.52(2H,m), 7.70-7.90(2H,m), 8.32 (1H,d,J=5.5Hz).

Synthetic Example 32

2-[[[5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl benzoate

[0444] To a solution (10 mL) of bis(trichloromethyl)carbonate (0.344 g) in tetrahydrofuran was dropwise added a solution (5 mL) of pyridine (0.281 mL) in tetrahydrofuran under ice-cooling, and the mixture was stirred at 0°C for 30 min. 2-(Methylamino)ethyl benzoate hydrochloride (0.750 g) obtained in Reference Example 5 was added to the re-

action mixture. A solution (5 mL) of triethylamine (0.485 mL) in tetrahydrofuran was added, and the mixture was stirred at 0°C for 1 hr. and at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure and water (30 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained oil was dissolved in tetrahydrofuran (5 mL), the mixture was added to a solution (10 mL) of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (1.0 g), triethylamine (0.808 mL) and 4-dimethylaminopyridine (0.071 g) in tetrahydrofuran, and the mixture was stirred at 40°C for 18 hrs. The reaction mixture was concentrated under reduced pressure and water (30 mL) was added to the residue. The mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate) to give a 1:1 mixture (1.50 g) of the title compound and 2-[[[6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl benzoate as a pale-yellow amorphous solid.
^{1}H-NMR ($CDCl_3$) : 2.05-2.35(6H,m), 3.00-3.30(3H,br), 3.60-4.40(8H,m), 4.60-5.10(4H,m), 6.80-7.00(2H,m), 7.20-7.70 (4H,m), 7.95-8.25(3H,m).

Synthetic Example 33

3-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] propyl benzoate

[0445] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., 3-(methylamino)propyl benzoate hydrochloride (1.38 g) obtained in Reference Example 32 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (25 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.63 g), triethylamine (1.23 mL) and 4-dimethylaminopyridine (0.054 g) were added, and the mixture was stirred at 60°C for 4 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (1.26 g) as a yellow amorphous solid.
^{1}H-NMR($CDCl_3$) : 2.21(3H,s), 2.20-2.30(2H,bm), 3.06 (3H,bs), 3.60-3.75(2H,bm), 4.36(2H,q,J=7.8Hz), 4.30-4.50(2H, bm), 4.80-5.15 (2H,bm), 6.62 (1H, d, J=5.7Hz), 7.26-7.44 (5H, m), 7.54 (1H,m), 7.81(1H,m), 7.93-8.03(2H,bm), 8.35 (1H,d,J=5.7Hz).

Synthetic Example 34

2-[Methyl[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl tetrahydropyran-4-yl carbonate

[0446] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 20 min., 2-(methylamino)ethyl tetrahydropyran-4-yl carbonate hydrochloride (1.43 g) obtained in Reference Example 17 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (20 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (20 mL). 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.63 g), triethylamine (1.23 mL) and 4-dimethylaminopyridine (0.027 g) were added, and the mixture was stirred at 60°C for 17.5 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (120 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1), then by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then 2:1). Crystallization from diethyl ether gave the title compound (1.23 g) as

a colorless solid.
^{1}H-NMR ($CDCl_3$) : 1.64-1.81 (2H,m), 1.92-2.03 (2H,m), 2.23 (3H,s), 3.10(3H,bs), 3.40-4.30(2H,br), 3.46-3.59 (2H,m), 3.87-3.99 (2H,m), 4.39 (2H,q,J=7.9Hz), 4.45 (2H,m), 4.77-5.15 (3H,m), 6.65 (1H,d,J=5.4Hz), 7.35-7.50 (3H,m), 7.85 (1H,m), 8.36 (1H,d,J=5.4Hz).

Synthetic Example 35

Ethyl 2-[methyl[[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate

[0447] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., ethyl 2-(methylamino)ethyl carbonate hydrochloride (1.10 g) obtained in Reference Example 14 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.63 g), triethylamine (1.23 mL), 4-dimethylaminopyridine (0.054 g) was added, and the mixture was stirred at 60°C for 14 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (30 mL), and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1), and then by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then 2:1) to give the title compound (1.27 g) as a yellow amorphous solid.
^{1}H-NMR($CDCl_3$) : 1.32(3H,t,J=7.1Hz), 2.23 (3H,s), 3.09 (3H,bs), 3.50-4.76(4H,br), 4.21(2H,q,J=7.1Hz), 4.38(2H,q, J=7.9Hz), 4.84-5.14(2H,m), 6.64(1H,d,J=5.6Hz), 7.36-7.46(3H,m), 7.83(1H,d,J=7.2Hz), 8.34(1H,d,J=5.6Hz).

Synthetic Example 36

Ethyl 2-[methyl[[(S)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate

[0448] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., ethyl 2-(methylamino)ethyl carbonate hydrochloride (1.10 g) obtained in Reference Example 14 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (30 mL), and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (S)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.15 g), triethylamine (0.87 mL) and 4-dimethylaminopyridine (0.035 g) were added, and the mixture was stirred at 60°C for 12 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1). Crystallization from diethyl ether gave the title compound (0.40 g) as a colorless solid.
^{1}H-NMR($CDCl_3$) : 1.32 (3H,t,J=7.2Hz), 2.23 (3H,s), 3.10 (3H,bs), 3.50-4.56(4H,br), 4.22(2H,q,J=7.2Hz), 4.38(2H,q, J=7.9Hz), 4.84-5.14 (2H,m), 6.65 (1H,d,J=5.6Hz), 7.34-7.50 (3H,m), 7.85 (1H,m), 8.36 (1H,d,J=5.6Hz).

Synthetic Example 37

Ethyl 2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](methyl)amino]ethyl carbonate

[0449] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., ethyl 2-(methylamino)ethyl carbonate hydrochloride (1.10 g) obtained in Reference Example 14 was added. A solution

(1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2.5 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine (1.44 g) synthesized by the method described in JP-A-63-146882, triethylamine (1.16 mL) and 4-dimethylaminopyridine (0.049 g) were added, and the mixture was stirred at 60°C for 6 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1). Crystallization from diethyl ether gave the title compound (0.721 g) as a colorless solid.

^{1}H-NMR ($CDCl_3$) : 1.25-1.34 (3H,m), 2.23 (6H,s), 3.15, 3.32 (total 3H,s), 3.72(3H,s), 3.90-4.53(9H,m), 4.86 (1H,d, J=13.4Hz), 4.95(1H,d,J=13.4Hz), 6.79(1H,d,J=8.7Hz), 7.95(1H,d,J=8.7Hz), 8.22(1H,s).

Synthetic Example 38

2-[[[5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](methyl)amino]ethyl acetate

[0450] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl acetate hydrochloride (0.922 g) obtained in Reference Example 2 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine (0.85 g) synthesized by the method described in JP-A-63-146882, triethylamine (0.70 mL) and 4-dimethylaminopyridine (0.025 g) were added, and the mixture was stirred at 60°C for 5 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (90 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1). Crystallization from diethyl ether gave the title compound (0.173 g) as a colorless solid.

^{1}H-NMR($CDCl_3$): 2.04,2.09 (total 3H,s), 2.24 (6H,s), 3.13,3.30 (total 3H,s), 3.45-3.97 (2H,m), 3.72 (3H,s), 3.97(3H,s), 4.15-4.50 (2H,m), 4.85(1H,d,J=13.1Hz), 4.96(1H,d,J=13.1Hz), 6.80(1H,d,J=8.9Hz), 7.96(1H,d,J=8.9Hz), 8.22(1H,s).

Synthetic Example 39

2-[[[5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](phenyl)amino]ethyl acetate

[0451] To a solution (10 mL) of bis(trichloromethyl)carbonate (0.291 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.243 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-anilinoethyl acetate hydrochloride (0.647 g) obtained in Reference Example 27 was added. A solution (1 mL) of triethylamine (0.419 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine (0.867 g) synthesized by the method described in JP-A-63-146882, triethylamine (0.697 mL) and 4-dimethylaminopyridine (0.020 g) were added, and the mixture was stirred at 60°C for 10 hrs. After concentration under reduced pressure, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1). Crystallization from diethyl ether gave the title compound (0.311 g) as a colorless solid.

^{1}H-NMR ($CDCl_3$) : 1.96(3H,s), 2.23(3H,s), 2.25(3H,s), 3.72(3H,s), 4.01(3H,s), 4.12-4.52(4H,m), 4.78-5.22(2H,m), 6.62 (1H,d,J=8.7Hz), 7.02-7.18(3H,m), 7.32-7.48(2H,m), 7.73(1H,d,J=8.7Hz), 8.26 (1H,s).

Synthetic Example 40

4-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] butyl acetate

[0452] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 4-(methylamino)butyl acetate hydrochloride (1.08 g) obtained in Reference Example 37 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.02 g), triethylamine (0.77 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60°C overnight. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (0.93 g) as a yellow amorphous solid.
^{1}H-NMR($CDCl_3$) : 1.65-1.85 (4H,m), 2.03 (3H,s), 2.23(3H,s), 3.02(3H,bs), 3.45-3.63(2H,m), 4.03-4.13(2H,m), 4.37(2H, q,J=7.8Hz), 4.85-5.13(2H,m), 6.64(1H,d,J=5.6Hz), 7.36-7.46(3H,m), 7.84(1H,d,J=8.4Hz), 8.35(1H,d,J=5.6Hz).

Synthetic Example 41

Ethyl 4-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl] amino]butyl carbonate

[0453] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., ethyl 4-(methylamino)butyl carbonate hydrochloride (1.27 g) obtained in Reference Example 39 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.26 g), triethylamine (0.95 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60°C overnight. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (1.08 g) as a yellow amorphous solid.
^{1}H-NMR($CDCl_3$) : 1.31 (3H,t,J=7.2Hz), 1.73-1.91 (4H,m), 2.23 (3H,s), 3.01 (3H,bs), 3.50-3.62(2H,m), 4.15-4.22(4H, m), 4.38(2H,q,J=7.8Hz), 4.87-5.13(2H,m), 6. 64 (1H,d,J=5.4Hz), 7.35-7.46(3H,m), 7.83(1H,d,J=7.8Hz), 8.35(1H,d, J=5.4Hz).

Synthetic Example 42

Ethyl 3-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl] amino]propyl carbonate

[0454] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., ethyl 3-(methylamino)propyl carbonate hydrochloride (1.18 g) obtained in Reference Example 44 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole

(1.10 g), triethylamine (0.83 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60°C overnight. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (0.88 g) as a yellow amorphous solid.

^{1}H-NMR ($CDCl_3$) : 1.29 (3H,t,J=7.2Hz), 2.10-2.20 (2H, m), 2.22(3H,s), 3.02(3H,bs), 3.55-3.77 (2H, m), 4.14-4.30 (4H, m), 4.37(2H,q,J=7.8Hz), 4.83-5.13 (2H,m), 6.64 (1H,d,J=5.6Hz), 7.35-7.46(3H,m), 7.82 (1H,d,J=8.1Hz), 8.35 (1H,d, J=5.6Hz).

Synthetic Example 43

3-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] propyl acetate

[0455] To a solution (40 mL) of bis(trichloromethyl)carbonate (1.19 g) in tetrahydrofuran was dropwise added a solution (2 mL) of pyridine (0.95 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 3-(methylamino)propyl acetate hydrochloride (1.90 g) obtained in Reference Example 42 was added. A solution (2 mL) of triethylamine (1.68 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (100 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (40 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.99 g), triethylamine (1.50 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60°C overnight. After concentration under reduced pressure, water (100 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (1.22 g) as a yellow amorphous solid.

^{1}H-NMR($CDCl_3$) : 1.97 (3H,s), 2.05-2.15 (2H,m), 2.22 (3H,s), 3.03(3H,bs), 3.42-3. 72 (2H,m), 4. 10-4.22 (2H,m), 4.37 (2H,q,J=7.8Hz), 4.85-5.13(2H,m), 6.64(1H,d,J=5.6Hz), 7.24-7.44(3H,m), 7.83(1H,d,J=7.5Hz), 8.35(1H,d,J=5.6Hz).

Synthetic Example 44

3-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] propane-1,2-diyl diacetate

[0456] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 3-(methylamino)propane-1,2-diyl diacetate hydrochloride (1.35 g) obtained in Reference Example 46 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.27 g), triethylamine (0.96 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60°C overnight. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted'with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (0.64 g) as a yellow amorphous solid.

^{1}H-NMR($CDCl_3$) : 2.05 (3H,s), 2.13 (3H,s), 2.23 (3H,s), 3.07(3H,bs), 3.42-3.95(2H,m), 4.06-4.43(2H,m), 4.38(2H,q, J=7.8Hz), 4.85-5.05(2H,m), 5.42-5.50(1H,m), 6.63-6.66 (1H,m), 7.38-7.51 (3H,m), 7.78-7.85(1H,m), 8.33-8.36 (1H,m).

Synthetic Example 45

Diethyl 3-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]propane-1,2-diyl biscarbonate

[0457] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., diethyl 3-(methylamino)propane-1,2-diyl biscarbonate hydrochloride (1.71 g) obtained in Reference Example 47 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.53 g), triethylamine (1.16 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60°C overnight. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (1.42 g) as a yellow amorphous solid.
^{1}H-NMR ($CDCl_3$) : 1.28-1.34 (6H,m), 2.22 (3H,s), 3.07 (3H,bs), 3.42-4.60(10H,m), 4.85-5.08(2H,m), 5.30-5.42 (1H,m), 6.62-6.64 (1H,m), 7.37-7.42(3H,m), 7.80-7.83 (1H,m), 8.32-8.35 (1H,m).

Synthetic Example 46

2-[[[5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl](methyl)amino]ethyl 3-chlorobenzoate

[0458] To a solution (7 mL) of bis(trichloromethyl)carbonate (0.194 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.162 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-(methylamino)ethyl 3-chlorobenzoate hydrochloride (0.50 g) obtained in Reference Example 7 was added. A solution (1 mL) of triethylamine (0.279 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2.5 hrs. After concentration under reduced pressure, water (15 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine (0.445 g) synthesized by the method described in JP-A-63-146882, triethylamine (0.357 mL) and 4-dimethylaminopyridine (0.012 g) were added, and the mixture was stirred at 60°C for 14 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue, and the mixture was extracted with ethyl acetate (70 mL). The ethyl acetate layer was washed with saturated brine (20 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (0.360 g) as a colorless amorphous solid.
^{1}H-NMR($CDCl_3$) : 2.21 (3H,s), 2.23 (3H,s), 3.32,3.38 (total 3H,s), 3.72(3H,s), 3.81(3H,s), 3.92-4.09(2H,m), 4.50-4.73 (2H,m), 4.87 (1H,d,J=13.4Hz), 4.94 (1H,d,J=13.4Hz), 6.77 (1H,d,J=8.8Hz), 7.36 (1H,m), 7.52 (1H,m), 7.80-8.03 (3H, m), 8.20 (1H, s).

Synthetic Example 47

2-[Methyl[2-[[[3-methyl-4-(2.2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate

[0459] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.582 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.485 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., 2-(methylamino)ethyl acetate hydrochloride (0.922 g) obtained in Reference Example 2 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2.5 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (25 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (15 mL). 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.10 g), triethyl-

amine (0.84 mL) and 4-dimethylaminopyridine (0.036 g) were added, and the mixture was stirred at 60°C for 4.5 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then 2:1) to give the title compound (1.18 g) as a colorless solid. ^{1}H-NMR($CDCl_3$) : 2.10 (3H,s), 2.24 (3H,s), 3.09 (3H,bs), 3.60-4.00(2H,br), 4.25-4.50(2H,m), 4.38(2H, q,J=7.8Hz), 4.84-5.18 (2H,m), 6.64 (1H,d,J=5.6Hz), 7.36-7.48(3H,m), 7.85 (1H,d,J=7.8Hz), 8.35 (1H,d,J=5.6Hz).

Synthetic Example 48

Ethyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate

[0460] A solution of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (130 g), triethylamine (63.8 mL), 4-dimethylaminopyridine (0.86 g) and 2-[(chlorocarbonyl)(methyl)amino]ethyl ethyl carbonate (84.8 g) obtained in Reference Example 34 in tetrahydrofuran (813 mL) was stirred at 45-50°C for 18 hrs. The reaction mixture was concentrated under reduced pressure and water (300 mL) was added to the residue, and the mixture was extracted with ethyl acetate (700 mL). The ethyl acetate layer was washed 3 times with saturated brine (300 mL), and anhydrous magnesium sulfate (130 g) and activated carbon (13 g) were added. The mixture was stirred at room temperature for 30 min. and filtrated. The filtrate was concentrated under reduced pressure and the residue was dissolved in diethyl ether (600 mL) containing triethylamine (0.49 mL), and the mixture was concentrated under reduced pressure. This step was further repeated twice. The obtained oily substance was dissolved in ethanol (200 mL) containing triethylamine (2.45 mL) and water (120 mL) was dropwise added under ice-cooling. The precipitated crystals were collected by filtration, washed 3 times with ice-cooled ethanol-water (volume ratio 1:1, 150 mL) and dried to give the title compound (172.2 g) as a colorless solid. ^{1}H-NMR($CDCl_3$) showed the same chart as with the compound obtained in Synthetic Example 14.

Synthetic Example 49

2-Ethoxyethyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate

[0461] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.43 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.35 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 10 min., 2-ethoxyethyl 2-(methylamino)ethyl carbonate hydrochloride (0.82 g) obtained in Reference Example 48 was added. A solution (1 mL) of triethylamine (0.60 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 days. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.63 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60°C for 6 hrs. and at room temperature for 11 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then ethyl acetate:hexane=7:3) to give the title compound (1.39 g) as a yellow amorphous solid.
^{1}H-NMR($CDCl_3$) : 1.19(3H,t,J=6.9Hz), 2.23 (3H,s), 3.09 (3H,bs), 3.40-4.20(2H,br), 3.53 (2H,q,J=6.9Hz), 3.63-3.69(2H, m), 4.27-4.34(2H,m), 4.39(2H,q,J=7.8Hz), 4.47(2H,m), 4.80-5.20(2H,m), 6.65 (1H,d,J=5.6Hz), 7.30-7.52 (3H,m), 7.84 (1H,d,J=7.5Hz), 8.35(1H,d,J=5.6Hz).

Synthetic Example 50

3-Methoxypropyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate

[0462] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.53 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.44 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 5 min.,

3-methoxypropyl 2-(methylamino)ethyl carbonate hydrochloride (0.82 g) obtained in Reference Example 49 was added. A solution (1 mL) of triethylamine (0.75 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.63 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60°C for 6 hrs. and at room temperature for 6 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then ethyl acetate:hexane=7:3). Crystallization from diethyl ether gave the title compound (0.70 g) as a colorless solid.
^{1}H-NMR($CDCl_3$) : 1.94 (2H,quintet,J=6.2Hz), 2.23 (3H,s), 3.09(3H,bs), 3.31 (3H,s), 3.40-4.20 (2H,br), 3.44 (2H,t, J=6.2Hz), 4.25(2H,t,J=6.5Hz), 4.38(2H,q,J=7.8Hz), 4.44 (2H,m), 4.80-5.20 (2H,m), 6.64 (1H,d,J=5. 6Hz), 7.35-7.48 (3H,m), 7.83 (1H,d,J=7.8Hz), 8.34 (1H,d,J=5.6Hz).

Synthetic Example 51

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl N,N-dimethylglycinate

[0463] 2-(Methylamino)ethyl N,N-dimethylglycinate dihydrochloride (1.06 g) obtained in Reference Example 50 was added to tetrahydrofuran (40 mL) and the mixture was stirred for a while, to which bis(trichloromethyl)carbonate (0.77 g) was added. After ice-cooling, a solution (5 mL) of triethylamine (2.17 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 3 hrs. The precipitated solid was filtered off and ethyl acetate (80 mL) was added. The mixture was washed with an ice-cooled aqueous sodium hydrogen carbonate solution (50 mL) and saturated brine (50 mL×2) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.63 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60°C for 6 hrs. and at room temperature for 3 days. 4-Dimethylaminopyridine (0.037 g) was added, and the mixture was further stirred at 60°C for 6 hrs. After concentration under reduced pressure, an aqueous sodium hydrogen carbonate solution (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate, then methanol:ethyl acetate=1:19). Crystallization from diethyl ether gave the title compound (0.41 g) as a colorless solid.
^{1}H-NMR ($CDCl_3$) : 2.23 (3H, s), 2.35 (6H, s), 3.08 (3H,bs), 3.21(2H,s), 3.50-4.20 (2H,br), 4.38(2H,q,J=7.8Hz), 4.44 (2H,m), 4.80-5.18(2H,m), 6.64 (1H,d,J=5.6Hz), 7.36-7.48(3H,m), 7.84 (1H,d,J=6.9Hz), 8.35 (1H,d,J=5.6Hz).

Synthetic Example 52

S-[2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl] amino]ethyl] thioacetate

[0464] S-[2-(Methylamino)ethyl] thioacetate hydrochloride (0.75 g) obtained in Reference Example 51 was added to tetrahydrofuran (30 mL) and the mixture was stirred for a while, to which bis(trichloromethyl)carbonate (0.66 g) was added. After ice-cooling, a solution (10 mL) of triethylamine (1.85 mL) in tetrahydrofuran was dropwise added and the mixture was stirred under ice-cooling for 30 min. and at room temperature for 30 min. The precipitated solid was filtered off and ethyl acetate (50 mL) was added to the filtrate. The mixture was washed with ice-cooled 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.96 g), triethylamine (0.54 mL) and 4-dimethylaminopyridine (0.032 g) were added, and the mixture was stirred at 60°C for 6 hrs. and at room temperature for 8 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (eluted with acetone:hexane=3:7, then acetone:hexane=7:3) to give the title compound (1.19 g) as a yellow amorphous solid.

^{1}H-NMR($CDCl_3$) : 2.23 (3H,s), 2.34 (3H,s), 3.10 (3H,bs), 3.22(2H,t,J=6.6Hz), 3.67(2H,m), 4.38(2H,q,J=7.8Hz), 4.80-5.20 (2H,m), 6. 64 (1H,d,J=5. 7Hz), 7.35-7.50 (3H,m), 7.83(1H,d,J=6.9Hz), 8.35 (1H,d,J=5.7Hz).

Synthetic Example 53

Ethyl 2-[2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethoxy]ethyl carbonate

[0465] To a solution (40 mL) of bis(trichloromethyl)carbonate (1.19 g) in tetrahydrofuran was dropwise added a solution (2 mL) of pyridine (0.95 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., ethyl 2-[2-(methylamino)ethoxy]ethyl carbonate hydrochloride (2.73 g) obtained in Reference Example 52 was added. A solution (2 mL) of triethylamine (1.68 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (100 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (40 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (2.80 g), triethylamine (2:11 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60°C overnight. After concentration under reduced pressure, water (100 mL) was added to the residue, and the mixture was extracted with ethyl acetate (100 mL). The ethyl acetate layer was washed with saturated brine (100 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (2.19 g) as a yellow amorphous solid.
^{1}H-NMR($CDCl_3$) : 1.28 (3H,t,J=7.2Hz), 2.24 (3H,s), 3.10 (3H,bs), 3.38-3.80 (6H,m), 4.18(2H,q,J=7.2Hz), 4.27-4.34 (2H,m), 4.38(2H,q,J=8.4Hz), 4.83-5.30(2H,m), 6.65(1H,d,J=5.7Hz), 7.35-7.50(3H,m), 7.84(1H,d,J=7.8Hz), 8.36(1H,d, J=5.7Hz).

Synthetic Example 54

Ethyl 2-[methyl[[2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethoxy]carbonyl]amino]ethyl carbonate

[0466] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.59 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.49 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., ethyl 2-[methyl[[2-(methylamino)ethoxy]carbonyl]amino]ethyl carbonate hydrochloride (1.71 g) obtained in Reference Example 53 was added. A solution (1 mL) of triethylamine (0.84 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.59 g), triethylamine (1.20 mL) and 4-dimethylaminopyridine (catalytic amount) were added, and the mixture was stirred at 60°C overnight. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give the title compound (1.62 g) as a yellow amorphous solid.
^{1}H-NMR($CDCl_3$) : 1.24-1.31 (3H,m), 2.24 (3H,bs), 2.97-2.99 (3H,m), 3.10 (3H,bs), 3.55-3.58 (2H,m), 4.09-4.50 (10H, m), 4.88-5.08(2H,m), 6.65 (1H,t,J=5.7Hz), 7.36-7.48(3H,m), 7.85 (1H,d,J=6.9Hz), 8.36 (1H,d,J=5.7Hz).

Synthetic Example 55

Ethyl 2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl carbonate

[0467] To a solution (10 mL) of bis(trichloromethyl)carbonate (0.291 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.243 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., ethyl 2-(methylamino)ethyl carbonate hydrochloride (0.551 g) obtained in Reference Example 14 was added. A solution (1 mL) of triethylamine (0.418 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2 hrs. After concentration under reduced pressure, water (15 mL) was added to the residue, and the mixture

was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (0.817 g), triethylamine (0.661 mL) and 4-dimethylaminopyridine (0.012 g) were added, and the mixture was stirred at 60°C for 12 hrs. After concentration under reduced pressure, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give a 3:2 mixture (0.92 g) of the title compound and ethyl 2-[[[6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl carbonate as a pale-yellow amorphous solid.

^{1}H-NMR ($CDCl_3$) : 1.27-1.34 (3H,m), 2.10-2.30 (3H,m), 2. 23 (3H, s), 2.99-3.23(3H,m), 3.40-3.85 (2H,m), 3.69 (6/5H, s), 3.71 (9/5H,s), 3.86(6/5H,s), 3.88(9/5H,s), 4.14-4.25(2H,m), 4.38-4.60(2H,m), 4.82-5.06(2H,m), 6.92-7.08(7/5H,m), 7.33(3/5H,d,J=9.0Hz), 7.66 (1H,m), 8.21 (1H,s).

Synthetic Example 56

2-[[[5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](phenyl)amino] ethyl acetate

[0468] To a solution (10 mL) of bis(trichloromethyl)carbonate (0.291 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.243 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-anilinoethyl acetate hydrochloride (0.647 g) obtained in Reference Example 27 was added. A solution (1 mL) of triethylamine (0.419 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (0.829 g), triethylamine (0.669 mL) and 4-dimethylaminopyridine (0.012 g) were added, and the mixture was stirred at 60°C for 14 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2) to give a 1:1 mixture (1.10 g) of the title compound and 2-[[[6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl)carbonyl](phenyl)amino] ethyl acetate as a colorless amorphous solid.

^{1}H-NMR ($CDCl_3$) : 1.99 (3H,s), 2.19 (1.5H.s), 2.21 (1.5H,s), 2.25(3H,s), 3.70 (1.5H,s), 3.71 (3H,s), 3.78 (1.5H,s), 3.84 (1.5H,s), 4.15-4.56(4H,m), 4.74-4.80 (1H,m), 4.91-4.98 (1H,m), 6.83-6.91 (1.5H,m), 7.04-7.19(3.5H,m), 7.25-7.53 (2.5H,m), 7.51 (0.5H,d,J=8.7Hz), 8.25 (1H,s).

Synthetic Example 57

Ethyl 2-[[[(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl] (methyl)amino]ethyl carbonate

[0469] To a solution (10 mL) of (S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (1.34 g) synthesized by the method described in Synthetic Example 1 of JP-A-10-504290 in tetrahydrofuran were added 2-[(chlorocarbonyl)(methyl)amino]ethyl ethyl carbonate (0.9 mL) obtained in Reference Example 34, triethylamine (1.08 mL) and 4-dimethylaminopyridine (0.010 g), and the mixture was stirred at 60°C for 6 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1) to give a 3:2 mixture (0.92 g) of the title compound and ethyl 2-[[[(S)-6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl carbonate as a pale-yellow amorphous solid.

^{1}H-NMR($CDCl_3$) : 1.25-1.34 (3H,m), 2.10-2.30 (3H,m), 2.23(3H,s), 2.99-3.23(3H,m), 3.40-3.85(2H,m), 3.69 (6/5H,s), 3.71 (9/5H,s), 3.86 (6/5H,s), 3.88 (9/5H,s), 4.14-4.25 (2H,m), 4.38-4.60(2H,m), 4.79-5.05(2H,m), 6.92-7.08(7/5H,m), 7.33(3/5H,d,J=9.3Hz), 7.65(1H,m), 8.21 (1H, s).

Synthetic Example 58

Ethyl 2-[[[2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino]ethyl carbonate

[0470] To a solution (10 mL) of bis(trichloromethyl)carbonate (0.291 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.243 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., ethyl 2-(methylamino)ethyl carbonate hydrochloride (0.551 g) obtained in Reference Example 14 was added. A solution (1 mL) of triethylamine (0.418 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 2.5 hrs. After concentration under reduced pressure, water (15 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 2-[[[4-(3-Methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.723 g), triethylamine (0.528 mL) and 4-dimethylaminopyridine (0.012 g) were added, and the mixture was stirred at 60°C for 17 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2), then by silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate) to give the title compound (0.44 g) as a colorless amorphous solid.
^{1}H-NMR($CDCl_3$) : 1.31(3H,t,J=7.1Hz), 2.05(2H,m), 2.18(3H,s), 3.08(3H,bs), 3.34(3H,s), 3.54 (2H,t,J=6.1Hz), 3.61-4.01(2H,m), 4.08(2H,t,J=6.3Hz), 4.21(2H,t,J=7.1Hz), 4.38-4.54(2H,m), 4.81-5.12(2H,m), 6.68(1H,d,J=5.6Hz), 7.34-7.48(3H,m), 7.83(1H,d,J=7.8Hz), 8.27(1H,d,J=5.6Hz).

Synthetic Example 59

2-[[[2-[[[4-(3-Methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](phenyl)amino]ethyl acetate

[0471] To a solution (10 mL) of bis(trichloromethyl)carbonate (0.291 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.243 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 30 min., 2-anilinoethyl acetate hydrochloride (0.647 g) obtained in Reference Example 27 was added. A solution (1 mL) of triethylamine (0.419 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 2-[[[4-(3-Methoxypropoxy)-3-methyl-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.877 g), triethylamine (0.641 mL) and 4-dimethylaminopyridine (0.012 g) were added, and the mixture was stirred at 60°C for 16 hrs. After concentration under reduced pressure, water (40 mL) was added to the residue, and the mixture was extracted with ethyl acetate (80 mL). The ethyl acetate layer was washed with saturated brine (15 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2), then by silica gel column chromatography (eluted with ethyl acetate) to give the title compound (0.93 g) as a colorless amorphous solid.
^{1}H-NMR ($CDCl_3$) : 1.99 (3H, s), 2.07 (3H. s), 2.19 (3H, s), 3.35(3H,s), 3.54(2H,t,J=6.2Hz), 4.09 (2H,t,J=6.2Hz), 4.14-4.40 (4H,m), 4.80(1H,d,J=13.7Hz), 5.00(1H,d,J=13.7Hz), 6.71(1H,d,J=5.7Hz), 7.03-7.34(7H,m), 7.38(1H,m), 7.65(1H,m), 8.32(1H,d,J=5.7Hz).

Synthetic Example 60

2-[[[5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](methyl)amino] ethyl ethyl carbonate

[0472] To a solution (8 mL) of bis(trichloromethyl)carbonate (0.174 g) in tetrahydrofuran was dropwise added a solution (1 mL) of pyridine (0.146 mL) in tetrahydrofuran under ice-cooling. After stirring under ice-cooling for 1 hr., ethyl 2-(methylamino)ethyl carbonate hydrochloride (0.330 g) obtained in Reference Example 14 was added. A solution (1 mL) of triethylamine (0.250 mL) in tetrahydrofuran was dropwise added, and the mixture was stirred at room temperature for 3 hrs. After concentration under reduced pressure, water (10 mL) was added to the residue, and the mixture was extracted with ethyl acetate (30 mL). The ethyl acetate layer was washed with saturated brine (10 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydro-

furan (8 mL). 5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole (0.432 g), triethylamine (0.279 mL) and 4-dimethylaminopyridine (0.008 g) were added, and the mixture was stirred at 60°C for 17.5 hrs. After concentration under reduced pressure, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (10 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:2, then 1:1), then by silica gel column chromatography (eluted with ethyl acetate:hexane=2:1, then ethyl acetate) to give a 1:1 mixture (0.09 g) of the title compound and 2-[[[6-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]methylamino]ethyl ethyl carbonate as a pale-yellow amorphous solid.

^{1}H-NMR($CDCl_3$) : 1.31 (3H,t,J=7.2Hz), 3.06 (3H,s), 3.42-3.98(2H,m), 3.87(3H,s), 3.90(3H,s), 4.21 (2H,q,J=7.2Hz), 4.36-4.54(2H,m), 4.90 (1H,d,J=13.2Hz), 4.98(1H,d,J=13.2Hz), 6.54(0.5H,t,J=73.5Hz), 6.61(0.5H,t,J=73.5Hz), 6.78 (1H,d,J=5.3Hz), 7.15-7.25(1.5H,m), 7.44(0.5H,d,J=9.0Hz), 7.59(0.5H,s), 7.80 (0.5H,d,J=9.0Hz), 8.17 (1H,d,J=5.3Hz).

Synthetic Example 61

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl 1-methylpiperidine-4-carboxylate

[0473] 2-(Methylamino)ethyl 1-methylpiperidine-4-carboxylate dihydrochloride (0.98 g) obtained in Reference Example 54 was added to tetrahydrofuran (50 mL) and the mixture was stirred for a while, to which bis(trichloromethyl) carbonate (0.53 g) was added. After ice-cooling, a solution (50 mL) of triethylamine (2.01 mL) in tetrahydrofuran was dropwise added and the mixture was stirred at room temperature for 3 hrs. Ethyl acetate (100 mL) was added and the mixture was washed with an aqueous sodium hydrogen carbonate solution (100 mL) and saturated brine (80 mL) and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (0.74 g), triethylamine (0.56 mL) and 4-dimethylaminopyridine (0.049 g) were added, and the mixture was stirred at 60°C overnight. After concentration under reduced pressure, an aqueous sodium hydrogen carbonate solution (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=7:3, then ethyl acetate, then methanol:ethyl acetate=1:19) to give the title compound (0.78 g) as a yellow-green amorphous solid.

^{1}H-NMR($CDCl_3$): 1.65-2.05 (6H,m), 2.23 (3H,s), 2.25 (3H,s), 2.24-2.38 (1H,m), 2.75-2.85 (2H,m), 3.07 (3H,bs), 3.40-4.10 (2H,br), 4.38(2H,q,J=7.8Hz), 4.40 (2H,m), 4.80-5.10 (2H,br), 6 .64 (1H,d,J=5.6Hz), 7.36-7.47 (3H,m), 7.84 (1H,d,J=7.8Hz), 8.35 (1H,d,J=5.6Hz).

Synthetic Example 62

2-[[4-(Aminocarbonyl)phenyl][[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate

[0474] To a solution (20 mL) of bis(trichloromethyl)carbonate (0.45 g) in tetrahydrofuran was dropwise added a solution (10 mL) of 2-[[4-(aminocarbonyl)phenyl]amino]ethyl acetate (0.67 g) obtained in Reference Example 55 and triethylamine (0.63 mL) in tetrahydrofuran under ice-cooling, and the mixture was stirred at room temperature for 1 hr. After concentration under reduced pressure, water (50 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with 0.2N hydrochloric acid (20 mL) and saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (30 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.63 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60°C for 30 min. and at room temperature overnight. After concentration under reduced pressure, an aqueous sodium hydrogen carbonate solution (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=4:6, then 6:4, then 8:2) to give the title compound (1.26 g) as a yellow amorphous solid.

^{1}H-NMR ($CDCl_3$) : 1.99 (3H, s), 2.26 (3H, s), 4.15-4.55 (4H,m), 4.41(2H,q,J=7.9Hz), 4.80-5.20 (2H, br), 6.69 (1H,d, J=5.7Hz), 7.26-7.38(3H,m), 7.48(2H,d,J=8.9Hz), 7.54(2H,d,J=8.9Hz), 7.66-7.73 (1H,m), 8.39 (1H,d,J=5.7Hz).

Synthetic Example 63

2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino] ethyl 1-methyl-4-piperidinyl carbonate

[0475] 2-(Methylamino)ethyl 1-methyl-4-piperidinyl carbonate dihydrochloride (1.01 g) obtained in Reference Example 56 was added to tetrahydrofuran (30 mL). After stirring for a while, the mixture was ice-cooled. Bis (trichloromethyl) carbonate (0.69 g) was added and a solution (10 mL) of triethylamine (1.95 mL) in tetrahydrofuran was dropwise added. After stirring under ice-cooling for 1 hr. and at room temperature for 1 hr., the precipitated solid was filtered off. After concentration under reduced pressure, ethyl acetate (50 mL) was added, and the mixture was washed with an ice-cooled aqueous sodium hydrogen carbonate solution (50 mL) and saturated brine (50 mL), and dried over anhydrous magnesium sulfate. The layer was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (20 mL). (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole (1.11 g), triethylamine (0.63 mL) and 4-dimethylaminopyridine (0.037 g) were added, and the mixture was stirred at 60°C overnight. After concentration under reduced pressure, an aqueous sodium hydrogen carbonate solution (50 mL) was added to the residue, and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (50 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=1:1, then ethyl acetate, then methanol:ethyl acetate=1:19) to give the title compound (0.70 g) as a yellow amorphous solid.
^{1}H-NMR($CDCl_3$) : 1.70-1.86 (2H,m), 1.90-2.04 (2H,m), 2.23 (3H,s), 2.28(3H,s), 2.10-2.35 (2H,m), 2.60-2.72 (2H,m), 3.08(3H,bs), 3.40-4.20(2H,br), 4.39 (2H,q,J=7.9Hz), 4.44(2H,m), 4.60-4.74 (1H,m), 4.80-5.15(2H,br), 6.65 (1H,d, J=5.9Hz), 7.35-7.52(3H,m), 7.84 (1H,d,J=7.5Hz), 8.35 (1H,d,J=5.9Hz).

Synthetic Example 64

2-[[4-(Aminocarbonyl)phenyl][[2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl] carbonyl]amino]ethyl acetate

[0476] To a solution (5 mL) of bis(trichloromethyl)carbonate (0.12 g) in tetrahydrofuran was dropwise added a solution (5 mL) of 2-[[4-(aminocarbonyl)phenyl]amino]ethyl acetate (0.22 g) obtained in Reference Example 55 and triethylamine (0.17 mL) in tetrahydrofuran under ice-cooling, and the mixture was stirred at room temperature for 30 min. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (30 mL). The ethyl acetate layer was washed with saturated brine (20 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in tetrahydrofuran (10 mL). 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl] sulfinyl]-1H-benzimidazole (0.37 g), triethylamine (0.28 mL) and 4-dimethylaminopyridine (0.012 g) were added, and the mixture was stirred at 60°C for 1 hr. After concentration under reduced pressure, an aqueous sodium hydrogen carbonate solution (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (30 mL). The ethyl acetate layer was washed with saturated brine (20 mL) and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate:hexane=3:7, then 5:5, then 8:2) to give the title compound (0.34 g) as a pale-yellow amorphous solid.
^{1}H-NMR ($CDCl_3$) : 1.99(3H,s), 2.26 (3H,s), 4.15-4.55(4H,m), 4.41(2H,q,J=7.9Hz), 4.80-5.20(2H,br), 6.69(1H,d, J=5.9Hz), 7.26-7.40(3H,m), 7.47(2H,d,J=8.8Hz), 7.54(2H,d,J=8. 8Hz), 7.65-7.74(1H,m), 8.38(1H,d,J=5.9Hz).

Synthetic Example 65

(-)-Ethyl 2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl]carbonyl] (methyl)amino]ethyl carbonate

[0477] 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine synthesized according to the method described in JP-A-63-146882 was subjected to preparative HPLC for optical resolution to give a (-) enantiomeric form (0.10 g) thereof. To a solution (5 mL) of this form in tetrahydrofuran were added 2-[(chlorocarbonyl)(methyl)amino]ethyl ethyl carbonate (0.081 g) obtained in Reference Example 34, triethylamine (0.080 mL) and 4-dimethylaminopyridine (0.007 g) and the mixture was stirred at 50°C for 18 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate: hexane=2:1) to give the title compound (0.053 g) as a colorless oil.
^{1}H-NMR($CDCl_3$): 1.30 (3H,t,J=7.1Hz), 2.24 (6H,s), 3.15,3.32 (total 3H,s), 3.73(3H,s), 3.90-4.55(9H,m), 4.85(1H,d,

J=13.2Hz), 4.97(1H,d,J=13.2Hz), 6.80(1H,d,J=8.8Hz), 7.96(1H,d,J=8.8Hz), 8. 23 (1H, s).

Synthetic Example 66

(+)-Ethyl 2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-3H-imidazo[4,5-b]pyridin-3-yl] carbonyl](methyl)amino]ethyl carbonate

[0478] 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridine synthesized according to the method described in JP-A-63-146882 was subjected to preparative HPLC for optical resolution to give a (+) enantiomeric form (0.10 g) thereof. To a solution (5 mL) of this form in tetrahydrofuran were added 2-[(chlorocarbonyl)(methyl)amino]ethyl ethyl carbonate (0.081 g) obtained in Reference Example 34, triethylamine (0.080 mL) and 4-dimethylaminopyridine (0.007 g) and the mixture was stirred at 50°C for 18 hrs. After concentration under reduced pressure, water (30 mL) was added to the residue and the mixture was extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with saturated brine (30 mL) and dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was purified by basic silica gel column chromatography (eluted with ethyl acetate: hexane=2:1) to give a 2:1 mixture (0.115 g) of the title compound and (+)-ethyl 2-[[[5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-imidazo[4,5-b]pyridin-1-yl]carbonyl](methyl)amino]ethyl carbonate as a colorless oil. ^{1}H-NMR ($CDCl_3$) : 1.20-1.38 (3H,m), 2.24 (6H,s), 3.08,3.15,3.33(total 3H,s), 3.73(3H,s), 3.88-4.55(9H,m), 4.78-5.05 (2H,m), 6.80,6.86(1H,d,J=8.8Hz), 7.76,7.96 (1H,d,J=8.8Hz), 8.21,8.22(total 1H,s).

[0479] In the following Comparative Examples 1 and 2, Examples 1 - 3 and Experimental Examples 1 and 2, optically active R form of lansoprazole (hereinafter to be referred to as Compound A) was used as an active ingredient. In Comparative Examples and Examples, cornstarch, lactose and hydroxypropylmethylcellulose used were the Japanese Pharmacopoeia 14th Edition compatible products.

Comparative Example 1

[0480] Compound A (450 mg) and HPMC (trade name: Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (1550 mg) were mixed in a mortar and 200 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet (comparative preparation 1) having a diameter of 8 mm.

Comparative Example 2

[0481] Compound A (450 mg), HPMC (trade name, Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (1085 mg) and methacrylic acid copolymer L (trade name: Eudragit L100, manufactured by Rohm Pharma) (465 mg) were mixed in a mortar and 200 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet (comparative preparation 2) having a diameter of 8 mm.

Comparative Example 3

[0482] Ethyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl] carbonyl]amino]ethyl carbonate obtained in Synthetic Example 14 (compound 14) (900 mg) and HPMC (trade name: Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (2600 mg) were mixed in a mortar and 350 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet (comparative preparation 3) having a diameter of 9 mm.

Example 1

[0483] Compound A (113 mg), lactose (303 mg), cornstarch (50 mg) and low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (35 mg) were mixed in a mortar and 50 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet having a diameter of 5 mm. Compound A (450 mg) and HPMC (trade name: Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (1550 mg) were mixed in a mortar and 150 mg of the obtained mixture was used as an outer shell, which was tableted with the obtained tablet as an inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet (preparation 1) having a diameter of 8 mm.

Example 2

[0484] Compound A (113 mg), lactose (303 mg), cornstarch (50 mg) and low-substituted hydroxypropylcellulose

(trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (35 mg) were mixed in a mortar and 50 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet having a diameter of 5 mm. Compound A (450 mg), HPMC (trade name: Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (1085 mg) and methacrylic acid copolymer L (trade name: Eudragit L100, manufactured by Rohm Pharma) (465 mg) were mixed in a mortar and 150 mg of the obtained mixture was used as an outer shell, which was tableted with the obtained tablet as an inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet (preparation 2) having a diameter of 8 mm.

Example 3

[0485] Compound A (225 mg), lactose (125 mg), cornstarch (50 mg) and low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (10 mg) were mixed in a mortar and 50 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet having a diameter of 5 mm. Compound A (225 mg), HPMC (trade name: TC-5R, manufactured by Shin-Etsu Chemical Co., Ltd.) (350 mg) and HPMC (trade name: TC-5S, manufactured by Shin-Etsu Chemical Co., Ltd.) (225 mg) were mixed in a mortar and 150 mg of the obtained mixture was used as a outer shell, which was tableted with the obtained tablet as an inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet having a diameter of 8 mm. Furthermore, Compound A (100 mg), lactose (300 mg), cornstarch (50 mg) and low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (50 mg) were mixed in a mortar and 100 mg of the obtained mixture was used as an outer shell, which was tableted with the obtained tablet as an inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet (preparation 3) having a diameter of 10 mm.

Example 4

[0486] 2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate obtained in Synthetic Example 1 (compound 1) (113 mg), lactose (303 mg), cornstarch (50 mg) and low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (35 mg) were mixed in a mortar and 50 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet having a diameter of 5 mm. Compound 1 (450 mg) and HPMC (trade name: Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (1550 mg) were mixed in a mortar and 150 mg of the obtained mixture was used as an outer shell, which was tableted with the obtained tablet as an inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet (preparation 4) having a diameter of 8 mm.

Example 5

[0487] 2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl 2-pyridinecarboxylate obtained in Synthetic Example 12 (compound 12) (113 mg), lactose (303 mg), cornstarch (50 mg) and low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (35 mg) were mixed in a mortar and 50 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet having a diameter of 5 mm. Compound 12 (450 mg) and HPMC (trade name: Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (1550 mg) were mixed in a mortar and 150 mg of the obtained mixture was used as an outer shell, which was tableted with the obtained tablet as an inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet (preparation 5) having a diameter of 8 mm.

Example 6

[0488] Compound 14 (113 mg), lactose (303 mg), cornstarch (50 mg) and low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (35 mg) were mixed in a mortar and 50 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet having a diameter of 5 mm. Compound 14 (450 mg) and HPMC (trade name: Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (1550 mg) were mixed in a mortar and 150 mg of the obtained mixture was used as an outer shell, which was tableted with the obtained tablet as an inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet (preparation 6) having a diameter of 8 mm.

Example 7

[0489] 2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl tetrahydropyran-4-yl carbonate obtained in Synthetic Example 18 (compound 18) (113 mg), lactose (303 mg), cornstarch (50 mg) and low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (35 mg) were mixed in a mortar and 50 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet having a diameter of 5 mm. Compound 18 (450 mg) and HPMC (trade name: Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (1550 mg) were mixed in a mortar and 150 mg of the obtained mixture was used as an outer shell, which was tableted with the obtained tablet as an inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet (preparation 7) having a diameter of 8 mm.

Example 8

[0490] 2-[Cyclohexyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate obtained in Synthetic Example 23 (compound 23) (113 mg), lactose (303 mg), cornstarch (50 mg) and low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (35 mg) were mixed in a mortar and 50 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet having a diameter of 5 mm. Compound 23 (450 mg) and HPMC (trade name: Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (1550 mg) were mixed in a mortar and 150 mg of the obtained mixture was used as an outer shell, which was tableted with the obtained tablet as an inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet (preparation 8) having a diameter of 8 mm.

Example 9

[0491] 2-[[[(R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl](phenyl)amino]ethyl acetate obtained in Synthetic Example 25 (compound 25) (113 mg), lactose (303 mg), cornstarch (50 mg) and low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (35 mg) were mixed in a mortar and 50 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet having a diameter of 5 mm. Compound 25 (450 mg) and HPMC (trade name: Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (1550 mg) were mixed in a mortar and 150 mg of the obtained mixture was used as an outer shell, which was tableted with the obtained tablet as an inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet (preparation 9) having a diameter of 8 mm.

Example 10

[0492] 2-[[2-(Acetyloxy)ethyl][[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl acetate obtained in Synthetic Example 29 (compound 29) (113 mg), lactose (303 mg), cornstarch (50 mg) and low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (35 mg) were mixed in a mortar and 50 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet having a diameter of 5 mm. Compound 29 (450 mg) and HPMC (trade name: Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (1550 mg) were mixed in a mortar and 150 mg of the obtained mixture was used as an outer shell, which was tableted with the obtained tablet as an inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet (preparation 10) having a diameter of 8 mm.

Example 11

[0493] Ethyl 4-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]butyl carbonate obtained in Synthetic Example 41 (compound 41) (113 mg), lactose (303 mg), cornstarch (50 mg) and low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (35 mg) were mixed in a mortar and 50 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet having a diameter of 5 mm. Compound 41 (450 mg) and HPMC (trade name: Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (1550 mg) were mixed in a mortar and 150 mg of the obtained mixture was used as an outer shell, which was tableted with the obtained tablet as an inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet (preparation 11) having

a diameter of 8 mm.

Example 12

[0494] 2-Ethoxyethyl 2-[methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl carbonate obtained in Synthetic Example 49 (compound 49) (113 mg), lactose (303 mg), cornstarch (50 mg) and low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (35 mg) were mixed in a mortar and 50 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet having a diameter of 5 mm. Compound 49 (450 mg), HPMC (trade name: Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (1550 mg) were mixed in a mortar and 150 mg of the obtained mixture was used as an outer shell, which was tableted with the obtained tablet as an inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet (preparation 12) having a diameter of 8 mm.

Example 13

[0495] 2-[Methyl[[(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazol-1-yl]carbonyl]amino]ethyl N,N-dimethylglycinate obtained in Synthetic Example 51 (compound 51) (113 mg), lactose (303 mg), cornstarch (50 mg) and low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (35 mg) were mixed in a mortar and 50 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet having a diameter of 5 mm. Compound 51 (450 mg) and HPMC (trade name: Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (1550 mg) were mixed in a mortar and 150 mg of the obtained mixture was used as an outer shell, which was tableted with the obtained tablet as an inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet (preparation 13) having a diameter of 8 mm.

Example 14

[0496] Compound 14 (400 mg), lactose (160 mg), cornstarch (80 mg) and low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (160 mg) were mixed in a mortar and 80 mg of the obtained mixture was tableted using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a tablet having a diameter of 6mm. Compound 14 (400 mg), HPMC (trade name: TC-5R, manufactured by Shin-Etsu Chemical Co., Ltd.) (700 mg), HPMC (trade name: Metolose 65SH-4000, manufactured by Shin-Etsu Chemical Co., Ltd.) (700 mg) and granulated sugar (400 mg) were mixed in a mortar and 220 mg of the obtained mixture was used as an outer shell, which was tableted with the obtained tablet as an inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet having a diameter of 9 mm. Furthermore, compound 14 (100 mg), lactose (250 mg), cornstarch (50 mg) and low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.) (100 mg) were mixed in a mortar and 50 mg of the obtained mixture was used as an outer shell, which was tableted with the obtained tablet as am inner core using a hydraulic pump press (manufactured by RIKEN SEIKI) to give a dry coated tablet (preparation 14) having a diameter of 10 mm.

Example 15

[0497] In the same manner as in Example 14, a diameter of 9 mm dry coated tablet comprising 40 mg of compound 14 in an inner core having a diameter of 6 mm, and 40 mg of compound 14 in an outer shell was obtained. The obtained dry coated tablet was coated with a compound 14-containing suspension having the following composition using a HI-COATER HC-LABO (manufactured by Freund Corporation) to give a preparation 15 coated with an outermost layer containing 10 mg of compound 14 per one dry coated tablet.

Composition of coating solution:	
hydroxypropylcellulose (trade name: HPC-SL, manufactured by Nippon Soda Co., Ltd.)	2.5 g
low-substituted hydroxypropylcellulose (trade name: L-HPC, manufactured by Shin-Etsu Chemical Co., Ltd.)	2.5 g
compound 14	10 g
purified water	105 g

Experimental Example 1

[0498] The drug dissolution property of the controlled release composition of the present invention, which contains release-controlled parts A and B, was evaluated by a dissolution test.

[0499] To be specific, preparations 1 and 2 obtained in Examples 1 and 2 were subjected to a dissolution test (Paddle Method, 0.1% sodium dodecylsulfate-containing phosphate buffer (pH 6.8, 500 mL, 100 rpm, using a sinker). As a control group, comparative preparations 1 and 2 obtained in Comparative Examples 1 and 2 were subjected to a similar dissolution test. The results are shown in Fig. 1.

[0500] From the comparison with comparative preparations, the controlled release composition of the present invention has been shown to have multistep releaseability. It has been also clarified that the releaseability of the active ingredient from the release-controlled part B can be controlled by changing the kind (composition) of the polymer contained in the release-controlled part B in the composition of the present invention.

Experimental Example 2

[0501] The drug dissolution property of the controlled release composition of the present invention, which contains release-controlled parts A, B and C, was evaluated by a dissolution test.

[0502] To be specific, preparation 3 obtained in Example 3 was subjected to a dissolution test (Paddle Method, 0.1% sodium dodecylsulfate-containing phosphate buffer (pH 6.8, 500 mL, 100 rpm, using a sinker). The results are shown in Fig. 2.

[0503] From the comparison with comparative preparations (see Fig. 1), the controlled release composition of the present invention has been shown to have multistep releaseability. It has been also clarified that the releaseability of the active ingredient from each release-controlled part can be controlled by changing the kind of the carrier contained in each release-controlled part and the ratio of the active ingredient in each release-controlled part, in the composition of the present invention.

Experimental Example 3

[0504] The preparation of the present invention was evaluated by dissolution property.

[0505] To be specific, preparation 14 obtained in Example 14 was subjected to a dissolution test (Paddle Method, 0.1% sodium dodecylsulfate-containing phosphate buffer (pH 6.8, 500 mL, 100 rpm, using a sinker). As a control example, comparative preparation 3 obtained in Comparative Example 3 was subjected to a similar dissolution test. From the results shown in Fig. 3, the controlled release composition of the present invention has been shown to have multistep releaseability of rapid release in the first stage, sustained release in the middle stage and more rapid release than in the middle stage in the last stage.

Experimental Example 4

[0506] The preparation of the present invention was evaluated by the absorbability.

[0507] To be specific, one tablet of preparation 14 obtained in Example 14 was orally administered to beagle dogs under fasting and changes in the drug blood concentration were evaluated. As a control example, similar evaluation was performed using comparative preparation 3 obtained in Comparative Example 3. From the results shown in Fig. 4, in comparative preparation 3 showing constant sustained release, the blood concentration decreased after 4 hr from administration, which has indicated lower absorption in the lower small intestine - large intestine. In contrast, the preparation 14 of the present invention maintained high blood concentration even after 4 hr from administration, which has clarified that a constant effective blood concentration is maintained for a long time.

Industrial Applicability

[0508] The controlled release composition of the present invention shows a drug release profile characterized by a sustained drug release in the first and middle stages or middle stage, and a more rapid drug release in the last stage, and therefore, when used as a preparation for oral administration, it can maintain an effective blood concentration for an extended period of time even for a drug that shows lower absorbability due to the lower drug dissolution property in the lower small intestine - near the large intestine when used as a conventional sustained-release preparation.

Claims

1. A controlled release composition showing release of an active ingredient controlled in two or more steps at different release rates, which comprises

   1) a release-controlled part A comprising a proton pump inhibitor as an active ingredient, which is capable of controlling release of the active ingredient to occur at a predetermined rate; and
   2) a release-controlled part B comprising a proton pump inhibitor as an active ingredient, which is capable of controlling release of the active ingredient to occur at a predetermined rate lower than the release rate of the release-controlled part A;

   wherein the release of the active ingredient from the release-controlled part B precedes the release of the active ingredient from the release-controlled part A.

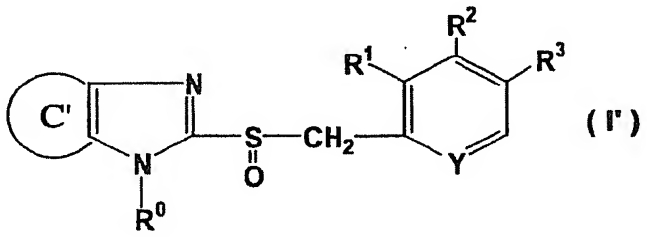
2. The controlled release composition of claim 1, further comprising a release-controlled part C comprising an active ingredient the same as or different from the active ingredient contained in the release-controlled part A and/or the release-controlled part B, which part C is capable of controlling release of the active ingredient to occur at a predetermined rate faster than the release rate of the release-controlled part B;
   wherein the release of the active ingredient from the release-controlled part C precedes the release of the active ingredient from the release-controlled part B.

3. The controlled release composition of claim 1 or 2,
   wherein the release-controlled part A is coated with the release-controlled part B.

4. The controlled release composition of claim 3, wherein the release-controlled part B is coated with the release-controlled part C.

5. The controlled release composition of claim 2, wherein the active ingredient contained in the release-controlled part C is a proton pump inhibitor.

6. The controlled release composition of any of claims 1 to 3, wherein the proton pump inhibitor contained in each release-controlled part is the same or different and each is a compound represented by the following formula (I'):



(I')

   wherein ring C' is a benzene ring optionally having substituent(s) or an aromatic monocyclic heterocycle optionally having substituent(s), R^0 is a hydrogen atom, an aralkyl group optionally having substituent(s), an acyl group or an acyloxy group, R^1, R^2 and R^3 are the same or different and each is a hydrogen atom, an alkyl group optionally having substituent(s), an alkoxy group optionally having substituent(s) or an amino group optionally having substituent(s), and Y is a nitrogen atom or CH,
   or a salt thereof or an optically active form thereof.

7. The controlled release composition of any of claims 3 to 5, wherein the proton pump inhibitor contained in each release-controlled part is lansoprazole or a prodrug thereof or a salt thereof or an optically active form thereof.

8. The controlled release composition of claim 2, wherein the active ingredient is contained in each release-controlled part in a weight ratio of A:5-95%, B:5-95% and C:0-40% (provided that when C:0%, the release-controlled part C does not exist).

9. The controlled release composition of claim 2, wherein the active ingredient is contained in each release-controlled

part in a weight ratio of A:20-75%, B:20-75% and C:5-30%.

10. The controlled release composition of claim 2, which is a solid composition for oral administration, wherein the release of the active ingredient contained in the release-controlled part C completes within 2 hr after administration.

11. The controlled release composition of claim 1 or 2,
wherein the release-controlled part B is a sustained-release matrix comprising an active ingredient and a hydrophilic polymer.

12. The controlled release composition of claim 1 or 2,
wherein the release-controlled part A is a sustained-release matrix comprising an active ingredient and a hydrophilic polymer.

13. The controlled release composition of claim 1 or 2,
wherein the release of the active ingredient from the release-controlled part B is maintained for 1-18 hr.

14. The controlled release composition of claim 1 or 2,
wherein the release of the active ingredient from the release-controlled part A is maintained for 30 min - 6 hr.

15. The controlled release composition of claim 2, wherein the release from the release-controlled part C is immediate release.

16. The controlled release composition of claim 1 or 2,
wherein the dosage form is selected from the group consisting of tablet, granule, pellet and capsule.

FIG. 1

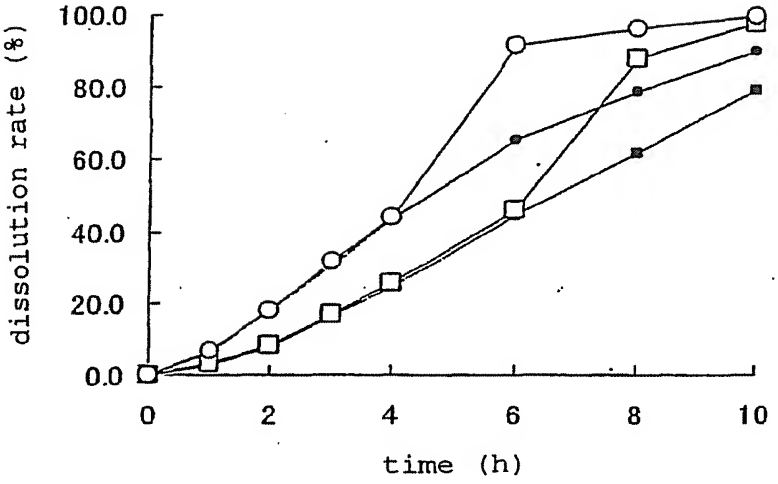


FIG. 2

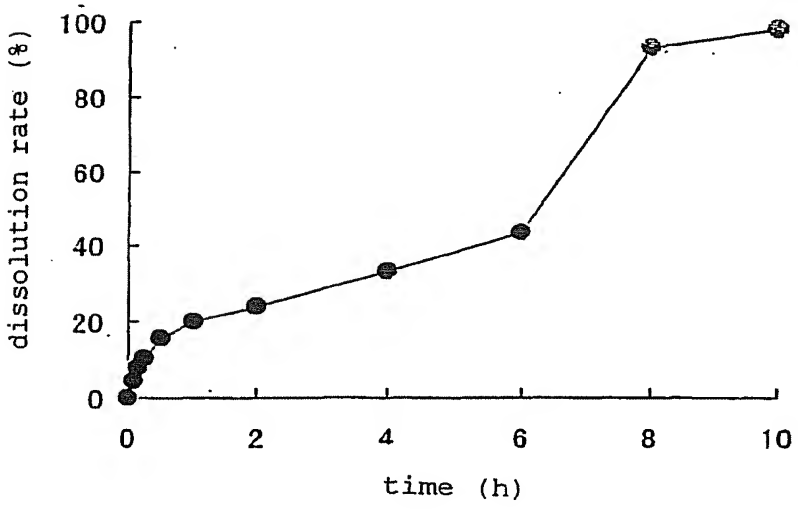


FIG. 3

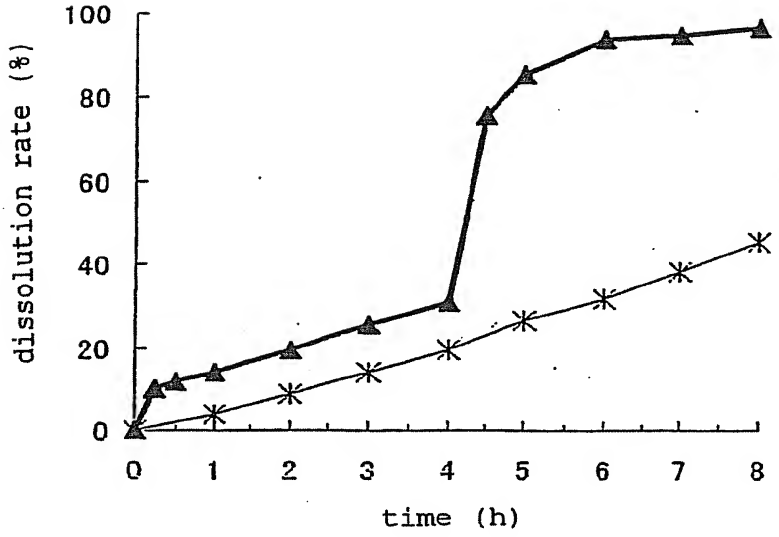
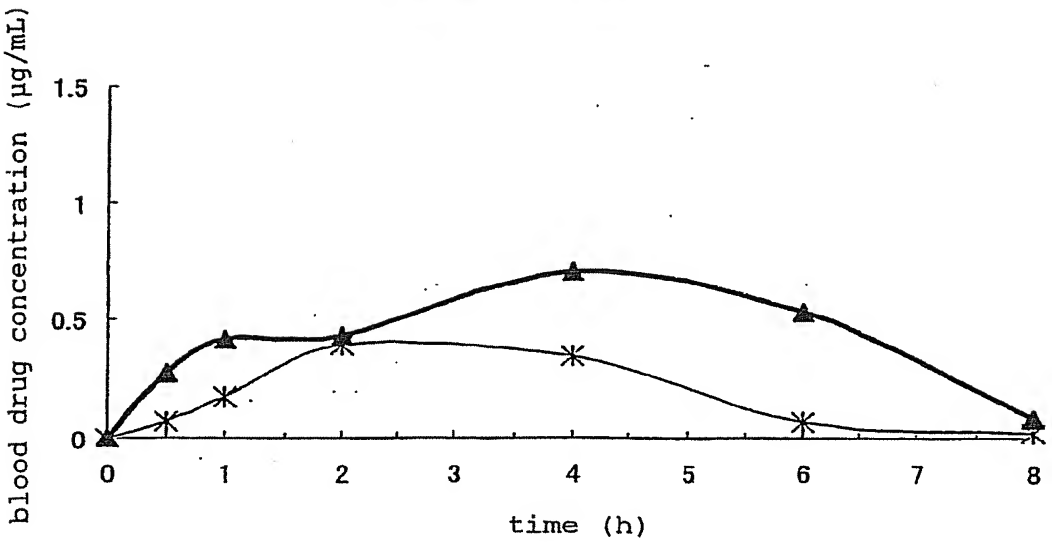


FIG. 4



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2004/003483

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] A61K9/22, 9/48, 9/16, 9/20, 45/00, A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] A61K9/00-72, 47/00-48, 45/00-45/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Jitsuyo Shinan Koho	1922-1996	Toroku Jitsuyo Shinan Koho	1994-2004
Kokai Jitsuyo Shinan Koho	1971-2004	Jitsuyo Shinan Toroku Koho	1996-2004

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN), EMBASE(STN), MEDLINE(STN), BIOSIS(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 6-11699 B2 (Bayer AG.), 16 February, 1994 (16.02.94), Full text; particularly, Claims 1 to 9; examples 1 to 23 & US 4892741 A	1-16
Y	JP 9-143073 A (Bayer Yakuhin, Ltd.), 03 June, 1997 (03.06.97), Full text; particularly, Claims 1 to 7; examples 1 to 4; Figs. 1, 2 & EP 776660 A2	1-16
Y	JP 2000-178193 A (Towa Yakuhin Kabushiki Kaisha), 27 June, 2000 (27.06.00), Full text; particularly, Claims 1 to 4; Fig. 1 (Family: none)	1-16

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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Date of the actual completion of the international search 12 May, 2004 (12.05.04)	Date of mailing of the international search report 25 May, 2004 (25.05.04)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2004/003483

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 2001-526211 A (Astra Zeneca AB.), 18 December, 2001 (18.12.01), Full text; particularly, Claims 1 to 23 & WO 99/32091 A1	1-16

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